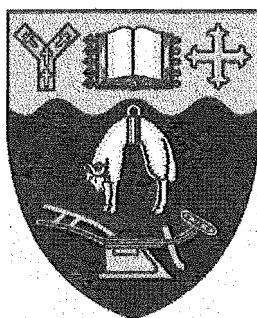


SYNTHETIC STUDIES ON THE TAXANE DITERPENOID

A thesis
submitted in partial fulfilment
of the requirements for the degree
of
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Andrew John Phillips



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ABSTRACT

This thesis describes synthetic studies aimed towards developing a concise synthesis of taxinine, a member of the taxane class of natural products. In **Chapter One**, an overview of the strategies used for the synthesis of this class of compounds is provided. A bicyclic enone was identified as a target for the studies described in this thesis. The strategy described also called for the addition of the C-ring by ring-closing metathesis.

A six step sequence to a C12-desmethyl A-ring is described in **Chapter Two**. The key step is the isomerization of an epoxide to an allylic alcohol. It was not possible to extend this chemistry to include C12-methylated substrates. An alternative Diels–Alder approach is also described. This approach allowed the synthesis of a number of C12-methylated A-ring structures.

A concise synthesis of diene precursors suitable for exploring the possibility of RCM as a method for the ring closure to form a taxane AB-ring system is described in **Chapter Three**. The planned ring-closing metathesis reaction was unsuccessful under a number of conditions examined.

An investigation described in **Chapter Four** delineates the use of ring-closing metathesis as a possible method for the introduction of the C-ring onto suitable AB-ring systems.

An alternative to the unsuccessful ring-closing metathesis approach, an intramolecular Diels–Alder synthesis of a bicyclo[4.3.1]decene system, is described in **Chapter Five**. Preliminary investigations into the ring-expansion of this compound are also described.

A brief summary and discussion of the future potential of the research conducted in this thesis is provided in **Chapter Six**.

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ABBREVIATIONS

18-C-6	18-crown-6
Ac	acetyl
Ar	aryl
b	broad (spectroscopic)
Bn	benzyl
BuLi	butyllithium
CI	chemical ionization (mass spectrometry)
COSY	correlation spectroscopy
δ	chemical shift in parts per million downfield from tetramethylsilane
d	doublet (spectroscopic)
DABCO	1,4-diazabicyclo[2.2.1]octane
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidone
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
EI	electron impact (in mass spectrometry)
ESI	electrospray ionisation (in mass spectrometry)
Et	ethyl
Et ₃ N	triethylamine
FAB	fast atom bombardment (in mass spectrometry)
g	gram(s)
GC	gas chromatography
h	hour(s)
HMBC	heteronuclear multiple bond coherence (in nmr)
HRMS	high-resolution mass spectrometry
HSMQC	heteronuclear single and multiple quantum coherence (in nmr)
HSQC	heteronuclear single quantum coherence (in nmr)
<i>J</i>	coupling constant (in nmr)
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilylamide

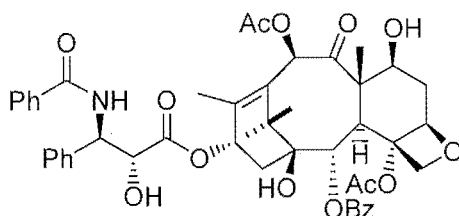
m	multiplet (spectroscopic), meter(s), milli
Me	methyl
min	minute(s)
m/z	mass to charge ratio (in mass spectrometry)
NCS	<i>N</i> -chlorosuccinimide
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Ph	phenyl
PhH	benzene
PhMe	toluene
ppm	parts per million (in nmr)
q	quartet (spectroscopic)
rt	room temperature
s	singlet (spectroscopic); second(s)
t	triplet (spectroscopic)
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBS	<i>tert</i> -butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TIPS	triisopropylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl, tetramethylsilane

Chapter One

Introduction: An Overview of Taxane Synthesis

1.1 Introduction

Paclitaxel[†] (**1**) is widely considered to be one of the most promising anticancer agents to appear in the past three decades. It represents a striking example of the difficulties involved in producing a clinically viable medicinal agent.¹



Paclitaxel, **1**

The history of paclitaxel is inextricably entwined with that of its source, the yew tree, which for centuries has provided humankind with weapons, poisons, and folk medicines. Chemists and biologists have written their own part of this rich history in

[†] Although commonly used in the scientific and popular literature for over 20 years, Taxol[™] was registered as a trademark by Bristol-Myers Squibb in 1993. A commentary on this topic can be found in *Nature* **1995**, 374, 432. The generic name is paclitaxel.

the last century. As a result of work in the laboratories of Lythgoe and Nakanishi, the structures of a number of constituents of the yew tree have been established and shown to share a diterpenoid carbon framework.² This carbon framework was named *taxane* (**Figure 1**) after the genus of the yew tree (*Taxus*) and members of this class of compounds are widely known as *taxanes*. A number of other illustrative examples are shown in **Figure 2**.

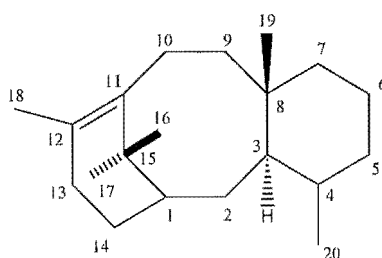


Figure 1 The taxane skeleton. The rings are usually denoted A, B, and C from left to right. In paclitaxel, the oxetane ring is labelled as the D-ring.

In the early 1960s the National Cancer Institute (USA) initiated a screening program designed to isolate new substances that exhibited anti-neoplastic activity. In 1962 Arthur Barclay, a United States Forest Service botanist, collected samples of the bark of the Pacific yew *Taxus brevifolia* Nutt. These samples were sent to Monroe Wall and Mankush Wani at the Research Triangle Institute in North Carolina where they were found to have significant cytotoxic activity.³ However, it was not until 1971 that the structure of the major cytotoxic component, paclitaxel, was elucidated by single crystal X-ray analysis of a 4-bromobenzoate derivative.⁴

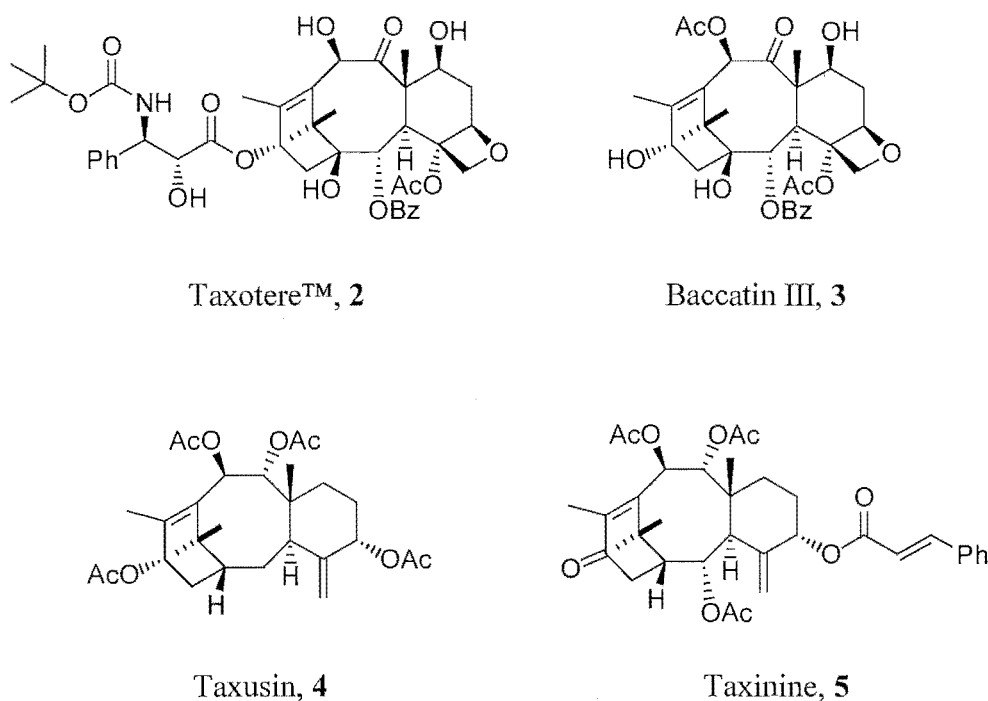


Figure 2 Illustrative members of the taxane family of diterpenoids. All are naturally occurring except the clinically relevant analog Taxotere™.

Further investigation of paclitaxel's merit as a therapeutic agent was hampered by limited supply, poor solubility, and the prominence of a number of other contemporary leads such as colchicine, camptothecin, and the vinca alkaloids.⁴ Nevertheless, seminal work by Susan Horowitz in 1979 revealed that paclitaxel was unique in its mode of action.⁵ Unlike other microtubule-active agents such as colchicine, maytansine, or vincristine, which act by destabilizing microtubules, paclitaxel was found to facilitate the assembly and stabilization of microtubules. Until the recent discovery of discodermolide,⁶ the epothilones,⁷ sarcodictyin A⁸ and eleutherobin⁹ (**Figure 3**), paclitaxel was the only known compound to have this mode of action.¹⁰

⁴ Paclitaxel demonstrated poor activity against solid tumors and commonly used cell-lines such as L1210 leukemia. However, it became apparent in the early 1970s that the most intensively studied models (such as L1210 leukemia and P388 leukemia), although valuable in the discovery of certain types of anti-cancer agents, were less useful for the discovery of agents of broad activity. It was the discovery in 1974 of paclitaxel's potent activity against the B16 melanoma cell line that stimulated further interest in paclitaxel's potential.³

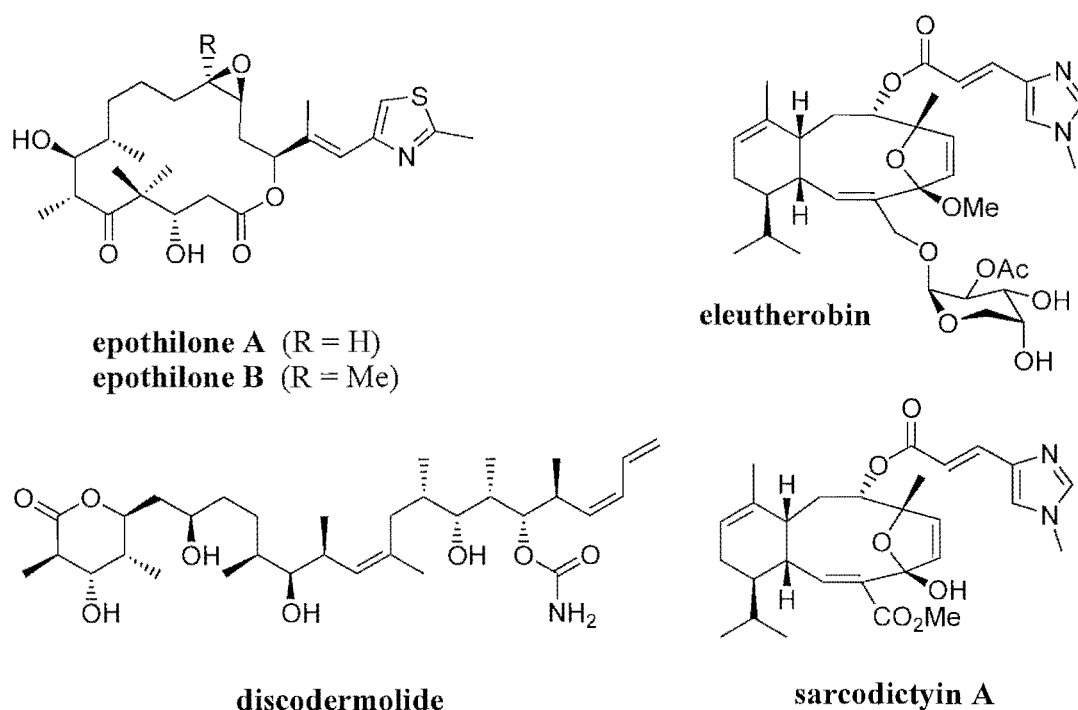


Figure 3 Selected natural products with tubulin polymerization and microtubule stabilization properties.

Encouraged by this result, the NCI progressed paclitaxel to phase I clinical trials in 1983. Despite continuing problems with supply and formulation, enough momentum was gained to see paclitaxel enter phase II trials in the late 1980s. It was here that paclitaxel's impressive activity in women with advanced ovarian cancer became clear. Women with metastases that were not responsive to other agents showed substantial response rates when treated with paclitaxel.¹¹ To facilitate further development and pave the way for FDA approval, the NCI signed an agreement with Bristol-Myers Squibb in 1991. In 1993, some two thousand years after the earliest mention of the yew tree as a source of biologically active compounds and a full 30 years after the discovery of the cytotoxic activity, paclitaxel was approved as a new medicinal agent for the treatment of ovarian cancer under the trade name TaxolTM.

Although always an issue, the question of supply has become more significant in recent years. Since 1993 paclitaxel has also been approved for the treatment of a number of

other cancers and current demand is greater than 300kg per year.¹² Initially paclitaxel was obtained from extraction of the bark of the Pacific yew. However, the yew tree is slow growing and the harvesting process results in the destruction of the tree. These issues, in combination with fear about potential damage to the delicate ecosystem in the Pacific Northwest of the United States, led to the exploration of other sources.[±]

Fortuitously, it was discovered that the leaves of the European yew *Taxus baccata* contained substantial amounts of baccatin III, a taxane that is readily converted to paclitaxel.¹³ This is the current source of both TaxolTM and Rhone-Poulenc Rorer's related, and clinically significant, drug TaxotereTM (see **Figure 2**).¹⁴ Nonetheless, a substantial amount of effort has been invested into exploring other possible sources. It has been shown that taxanes can be isolated from plant cell culture and more recently a taxane producing fungus, *Taxamyces sp.* has been identified. It is also possible that the enzymes responsible for the production of paclitaxel could be identified, cloned and expressed in bacterial systems to provide taxanes.¹⁵

In contrast to the above approaches to the supply of paclitaxel, total synthesis could potentially offer a flexible source, and perhaps more importantly, give access to analogues that may exhibit improved therapeutic profiles. It is clear that the current state of the art in organic synthesis is capable of preparing molecules of the complexity of paclitaxel (*vide infra*).¹⁶ However, to serve either as a source of paclitaxel or as a viable route to analogues these syntheses must be practical. Development of a practical synthesis of *any of the taxanes* will require the invention of new reactions, synthetic methods and/or strategies.

[±] To meet a demand of *ca* 300kg per year, some 750 000 yew trees would have to be felled. The US Forest Service estimates that there are 130 million yew trees in the Pacific Northwest of the United States.¹²

1.2 Structural Considerations

As a target for total synthesis the taxanes present a significant challenge. For example, paclitaxel has a tricyclo[9.3.1.0^{3,8}]pentadecene core punctuated by an array of functionality including an oxetane ring, a carboxylic acid side-chain, and numerous oxygenated carbons. The combination of these functional groups, along with a challenging carbocyclic skeleton, has meant that the taxanes have generated much interest as synthetic targets in the past decade.

Perhaps the most obvious synthetic challenge is the central eight-membered B-ring. Although numerous methods exist for the construction of five-, six- and seven-membered carbocycles,¹⁷ methods for eight-membered rings remain relatively underdeveloped.¹⁸

The A- and C-rings also present difficulties. For example, the C-ring of the taxanes is varied in its degree of oxygenation and it is linked to the B-ring by a *trans* ring junction. Both of these features are potential sources of difficulty. The A-ring contains a tetra-substituted bridgehead alkene. Contrary to some popular belief,¹⁹ this alkene is not anti-Bredt. Nonetheless, the regiospecific installation of this bond is a potential source of problems.

Inspection of the three-dimensional structure of paclitaxel[†] (**Figure 4**, see over page) reveals a number of features that are important in terms of synthetic planning. As can be seen, the A-ring assumes a boat conformation, the B-ring exists in a chair-boat conformation, and the C-ring is in a half-chair arrangement. Overall, the molecule assumes a cup-like shape. Although other conformers are possible, it is likely that this gross three-dimensional structure is typical of the paclitaxel core ring system and also of other taxanes.²⁰

[†] The author would like to thank Professor Don Mastropaolo (University of Washington) for providing the coordinates for paclitaxel. See ref 21.

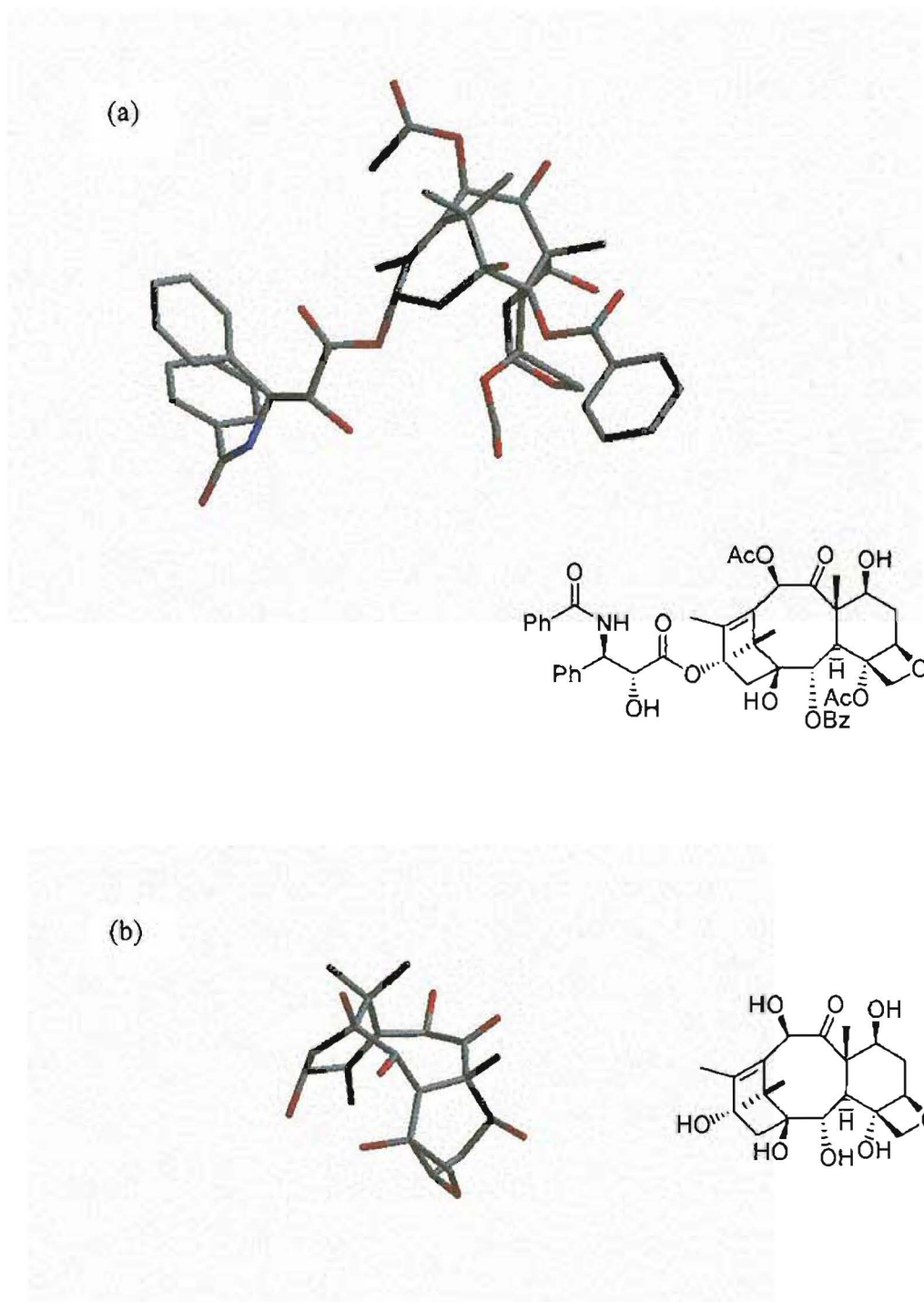


Figure 4 (a) The three dimensional structure of paclitaxel, **1**. A schematic of the structure is also shown for clarity. (b) The three dimensional structure of paclitaxel without acyl groups. The cup shape of the molecule is more evident in this simplified structure.²¹

As revealed by the three-dimensional structure, a number of functional groups that appear to be distant in the two-dimensional structure are, in reality, spatially close. For example, the proximity of the *gem*-dimethyl group and the C19 methyl group suggests that the introduction of these groups could be hampered by mutual steric repulsion.

The proximity of many functional groups means that the taxanes are prone to rearrangement reactions. This propensity to give unexpected products means that the protection of [potentially] reactive functionality is a significant feature of most synthetic strategies directed towards the taxanes. A great deal of information in this area has been gleaned from the extensive efforts of Shu-Hui Chen and Vittorio Farina (both at Bristol-Myers Squibb) in modifying paclitaxel.²² For example, the proximity of the C2 oxygen and the oxetane ring causes facile tetrahydrofuran formation when paclitaxel is subjected to Lewis acids such as tributyltin methoxide (**Figure 5**).²³

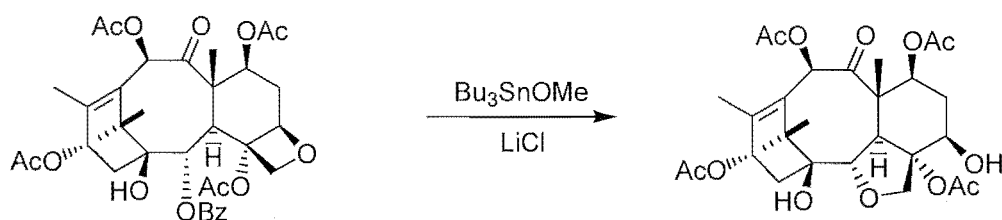


Figure 5 Proximity-induced reactions of the taxane skeleton when treated with Lewis acids

Substantial problems have also been encountered when taxanes are subjected to radical deoxygenation conditions (**Figure 6**).²⁴ However, perhaps the best known examples of the reactivity of paclitaxel are (i) the ring-contraction and oxetane opening reactions under acidic conditions,²⁵ and (ii) the epimerization of the C7 hydroxy group under basic conditions (**Figure 7**).²⁶ Notwithstanding these problems, it has proven possible to modify taxanes if extremes of conditions are avoided and due caution with respect to functional group protection is exercised.

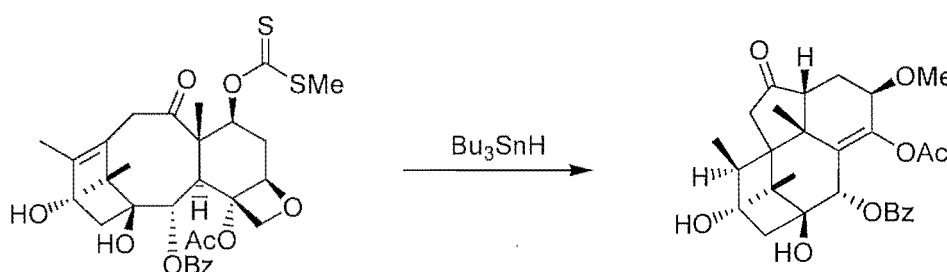


Figure 6 The polycyclic product formed upon attempts to deoxygenate C7 of a paclitaxel derivative – a further example of proximity-induced reactivity.

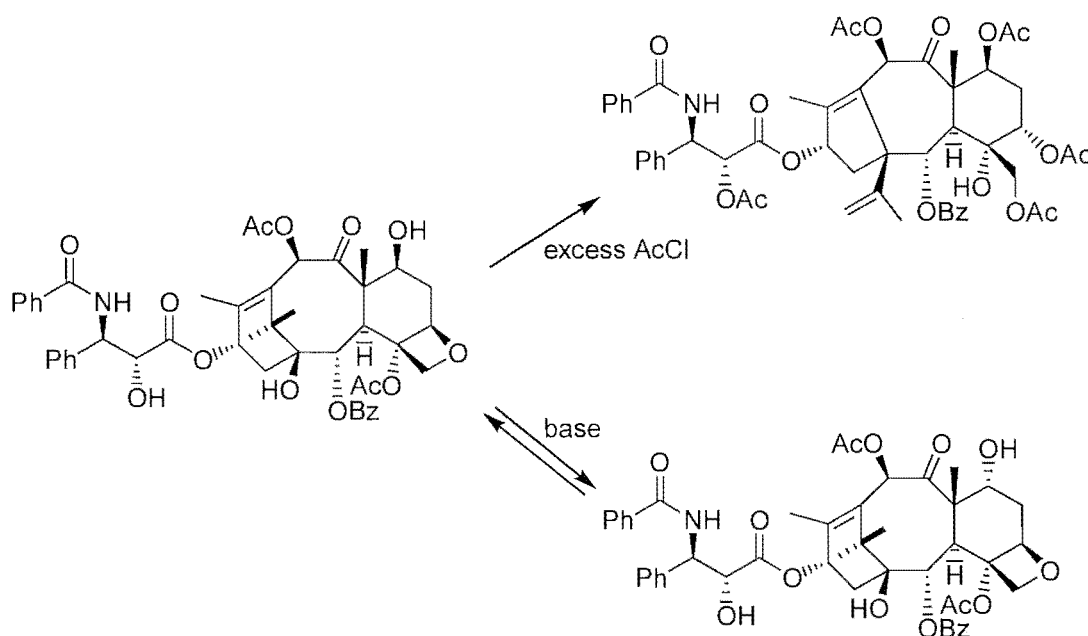


Figure 7 Reactivity of paclitaxel under acidic and basic conditions: ring contractions, ring openings, and epimerization.

1.3 Total Syntheses of Taxanes

So as to provide an historical perspective of the development of this area, the nine current total syntheses of taxanes are presented in chronological order.

1.3.1 Holton (*ent*-Taxusin, 1988)

The first synthesis of a member of the taxane class was achieved by Holton's group in 1988 when they prepared *ent*-taxusin (**4**, **Figure 2**).²⁷ The cornerstone of this synthesis was the fragmentation of bicyclic epoxy alcohols, a process that had been developed previously in the Holton laboratories (**Figure 8**).²⁸

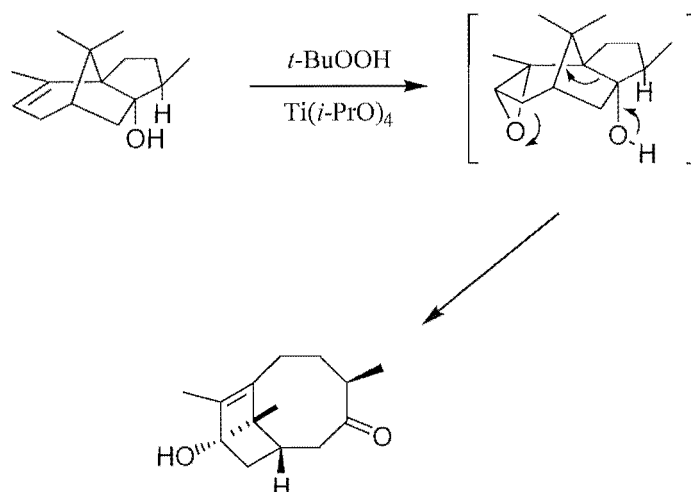


Figure 8 Holton's fragmentation of bicyclic epoxy alcohols.

Based on this work, the total synthesis of *ent*-taxusin began with a 10-step sequence which elaborated (-)- β -patchoulene oxide (**6**, sold as PatchinoTM by International Flavors and Fragrances, Inc.) into triol **7** (**Figure 9**). Epoxidation, followed by fragmentation, gave bicyclic ketone **8** which contains all of the necessary functionality and stereochemistry to allow subsequent annelation of the C-ring. A 9-step sequence gave the key tosylate **9** which underwent intramolecular alkylation to give tricyclic

ketone **10**. A short sequence involving enol ether oxidation, deprotection, acetylation and olefination gave *ent*-taxusin.

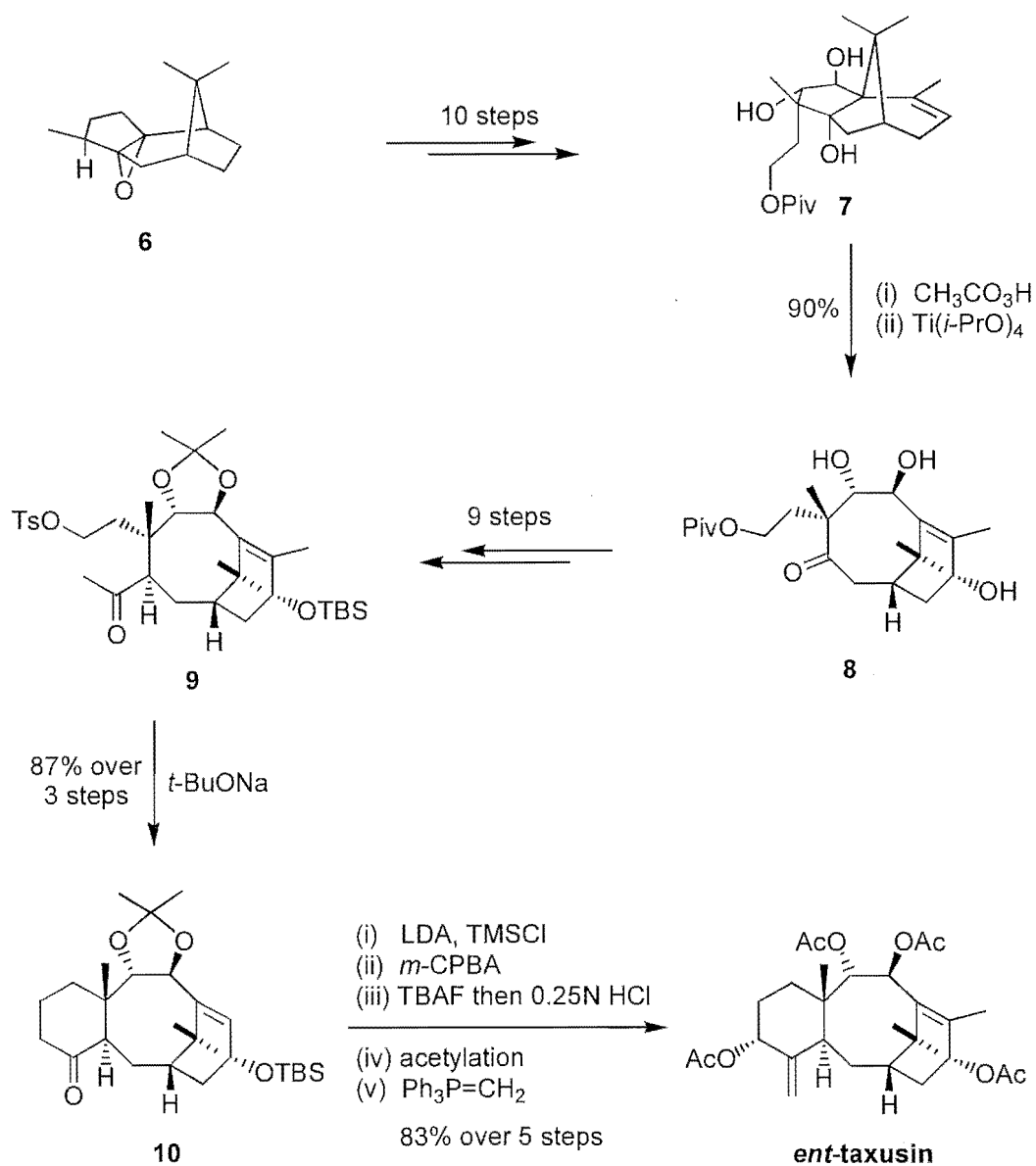


Figure 9 The Holton synthesis of *ent*-taxusin.

Although lengthy (*ca* 30 steps from PatchinoTM) the Holton synthesis of *ent*-taxusin is an elegant example of the use of small rings to control functional group manipulations and stereochemistry. This control allows the synthesis of a heavily functionalized bicyclic substrate which is readily fragmented. The major problem with this approach

is the elaboration of the C-ring (the Wender synthesis of paclitaxel is a further example of the problems associated with this type of strategy, *vide infra*). The problems encountered with this functionalization means that the addition of three carbons and two stereogenic centers to the skeleton requires *ca* 15 steps.

1.3.2 Holton (Paclitaxel, 1993)

The Holton synthesis of paclitaxel²⁹ was the first to be achieved and it utilized a great deal of the chemistry developed during the synthesis of *ent*-taxusin. The initial stages paralleled the route for *ent*-taxusin (Figure 10).

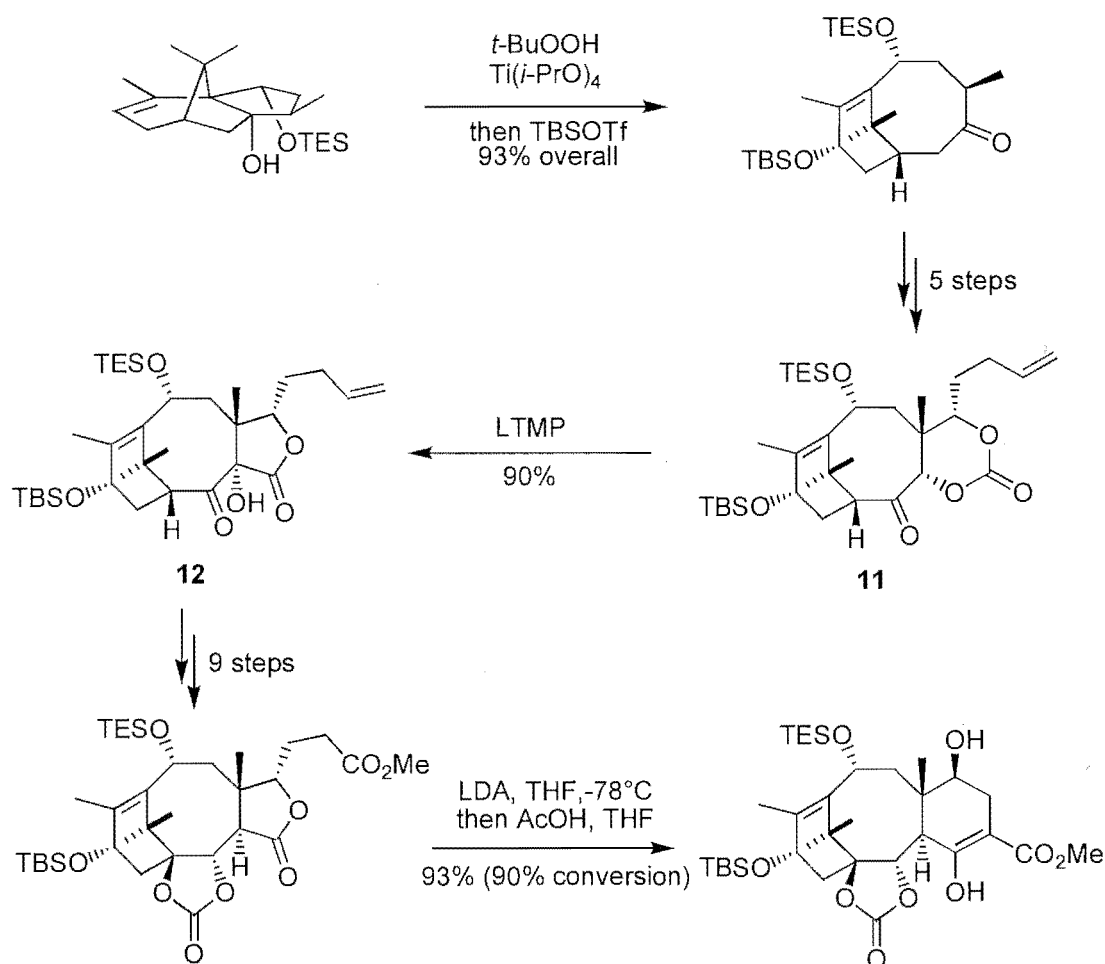


Figure 10 The initial stages of the Holton synthesis of paclitaxel.

Of note is the clever use of a Chan rearrangement (**11** to **12**) for the installation of the required one carbon unit for the formation of the C-ring. The key intermediate **A** was readily advanced to paclitaxel by a number of standard transformations (**Figure 11**) including formation of the oxetane ring by S_N2 displacement of a secondary tosylate.

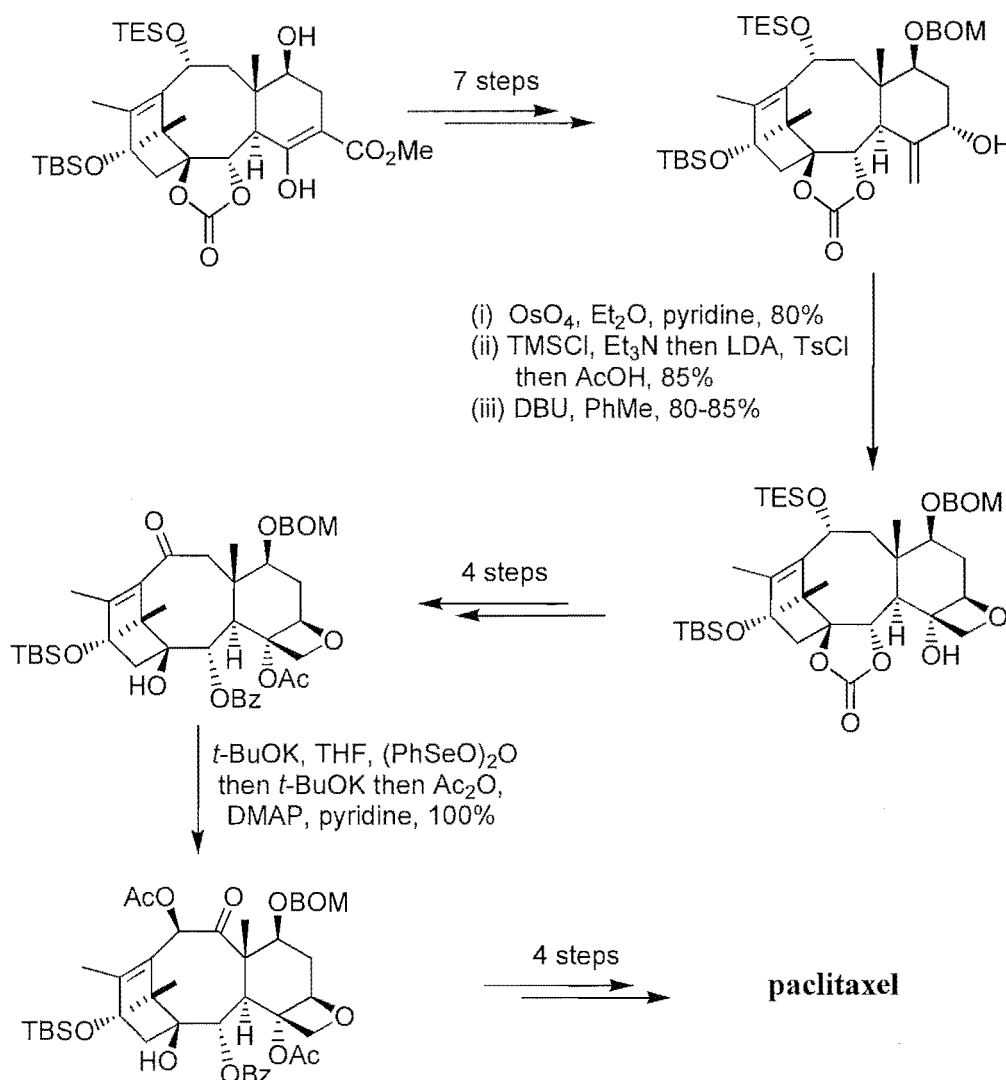


Figure 11 The closing steps of Holton's paclitaxel synthesis.

The route developed for paclitaxel—as was the case for Holton's synthesis of *ent*-taxusin—provides an illustration of the use of careful control of conformation to allow selective functionalization and reaction. A great deal of effort has also been invested into careful optimization of each reaction and the final overall yield is very impressive.

However, the length of the synthesis (*ca* 45 steps) is a major drawback. This feature alone precludes its use as a method of producing useful quantities of paclitaxel and the linear strategy also detracts from its merits as a means of producing analogues.

1.3.3 Nicolaou (Paclitaxel, 1993)

The Nicolaou synthesis of paclitaxel³⁰ involved a convergent strategy that used a McMurry-type pinacol coupling to form the central eight-membered ring as the key step. This strategy for taxane synthesis was first disclosed by Kende in 1986.³¹ As shown in **Figures 12** and **13**, Diels-Alder chemistry was used to assemble both A- and C-ring building blocks. The originally designed pyrone Diels-Alder reaction for the synthesis of C-ring intermediates gave the wrong regiochemistry. However, a beautiful solution to this problem was found in chemistry developed by Narasaka and reaction of the substrates in the presence of phenylboronic acid gave the desired compound.

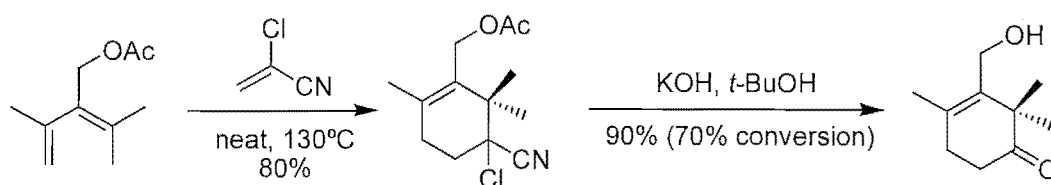


Figure 12 The Nicolaou A-ring synthesis by Diels-Alder chemistry.

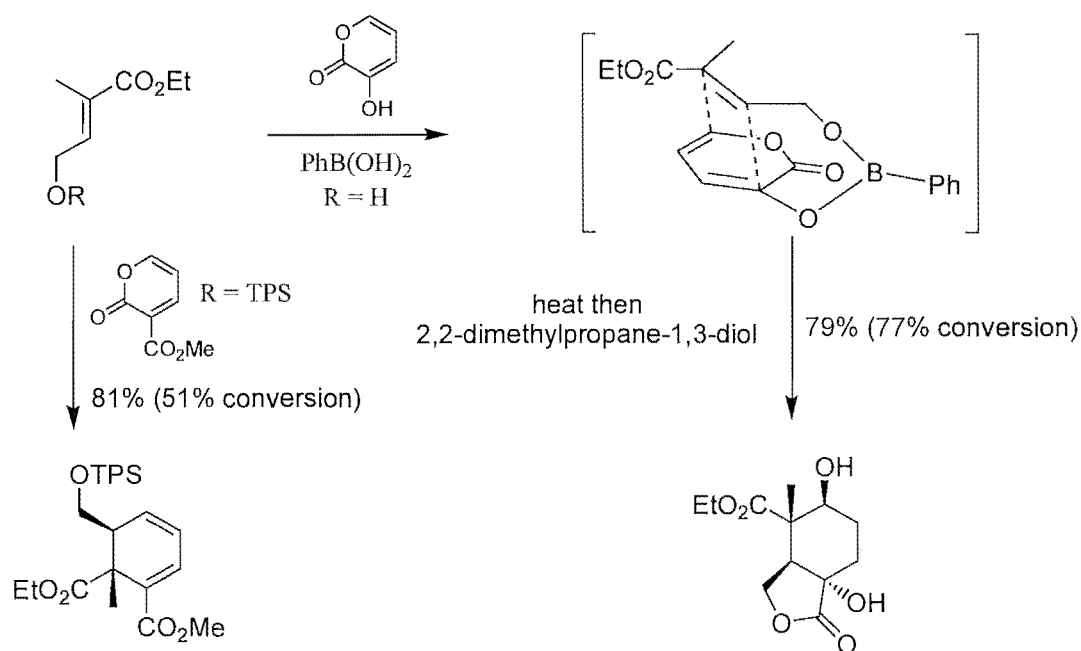


Figure 13 The use of Narasaka phenylboronic acid templates in the Nicolaou synthesis of taxane C-rings.

The A-ring and C-ring building blocks were coupled together by using an A-ring vinyl anion generated by Shapiro-type chemistry and a C-ring aldehyde (as shown in **Figure 14**). This process provided the required functionality to install the C1 hydroxy group with good control of stereochemistry. Further manipulation allowed the preparation of dialdehyde **13** which was subjected to McMurry-type reaction conditions (Zn/Cu couple and TiCl₃) to give diol **14**. This diol was readily resolved as the camphanate ester and advanced to paclitaxel *via* a long sequence that involved formation of the oxetane, phenyllithium attack on the cyclic C1-C2 carbonate and a number of deprotection and acylation steps.

Although conceptually versatile, the Nicolaou route is hampered by a number of problems. Clearly the use of the McMurry-type coupling in this setting is less than ideal. The yields of *ca* 25% for this key step are too low to allow further development of a route that still requires 19 steps (including a resolution) to reach paclitaxel. Another significant problem is the extensive manipulation of protecting groups and

oxidation level late in the synthesis. The combination of these, and other problems, lead to a very protracted synthesis (*ca* 50 steps).

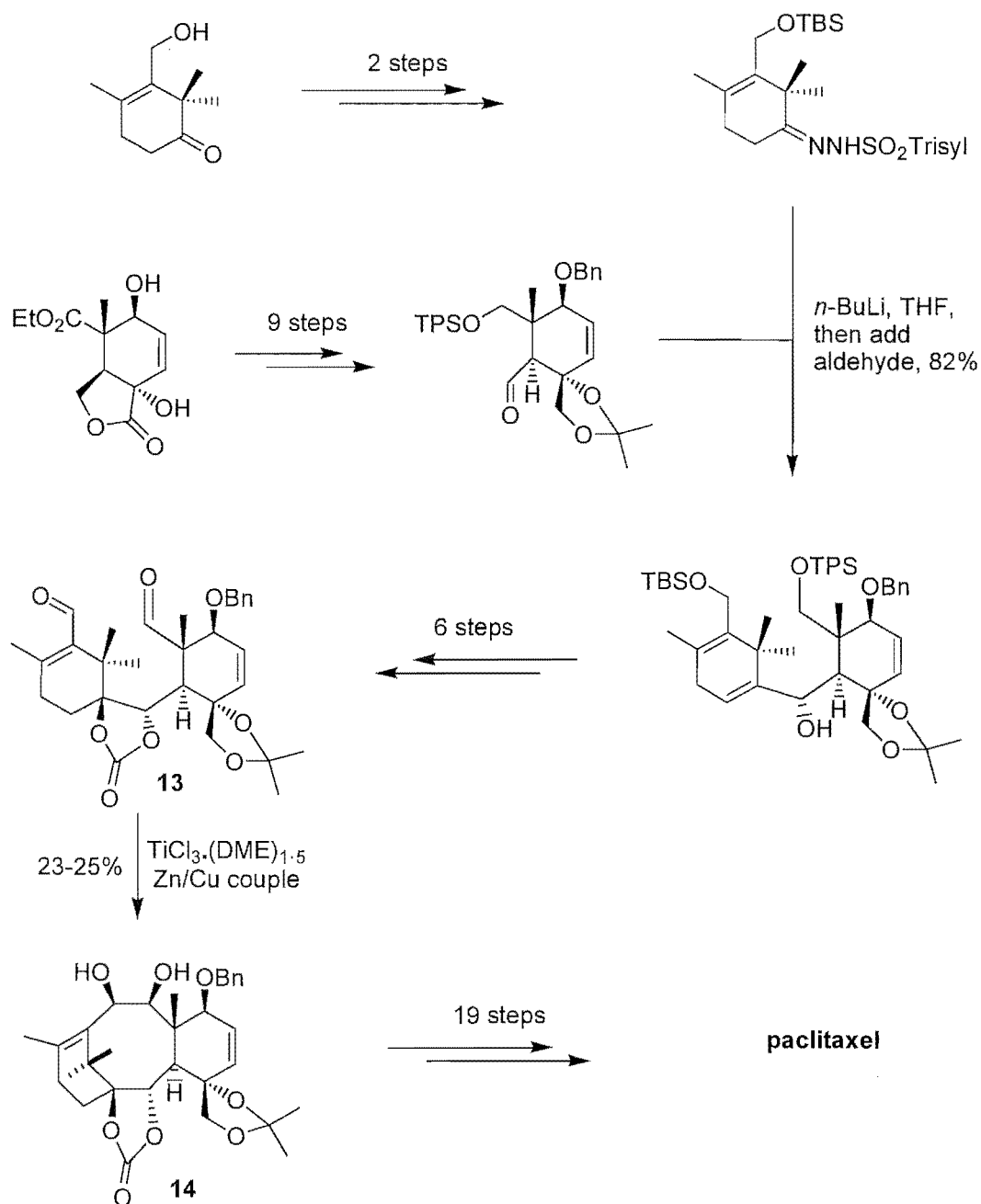


Figure 14 The Nicolaou synthesis of paclitaxel.

1.3.4 Danishefsky (Paclitaxel, 1995)

The Danishefsky group was particularly active in the taxane synthesis area, and in late 1995 these efforts resulted in what is arguably the benchmark for paclitaxel synthesis.³² Their venture began with enantiomerically pure (+)-Wieland-Miescher ketone (**15**) (**Figure 15**). This ketone was transformed into allylic alcohol **16** by a 10 step sequence consisting of standard transformations. The oxetane was installed by an S_N2 displacement strategy, developed simultaneously in the Danishefsky³³ and Potier³⁴ laboratories, that has been subsequently adopted by all the groups that have completed paclitaxel syntheses. The oxetane-containing alcohol was then elaborated into a fully functionalized (albeit in protected form) C-ring precursor. The A- and C-ring subunits were coupled together (**Figure 16**) by a strategy similar to that employed by Nicolaou, and the resultant B-*seco* compound was concisely manipulated into intramolecular Heck reaction substrate **17**. The pivotal ring-closure was achieved by treatment of this compound with Pd(PPh₃)₄ to give the desired tetracycle **18** in 49% yield. This compound was advanced to paclitaxel by a 15 step sequence that, after the somewhat problematic excision of the exocyclic methylene group, parallels the final steps of the Holton and Nicolaou syntheses.

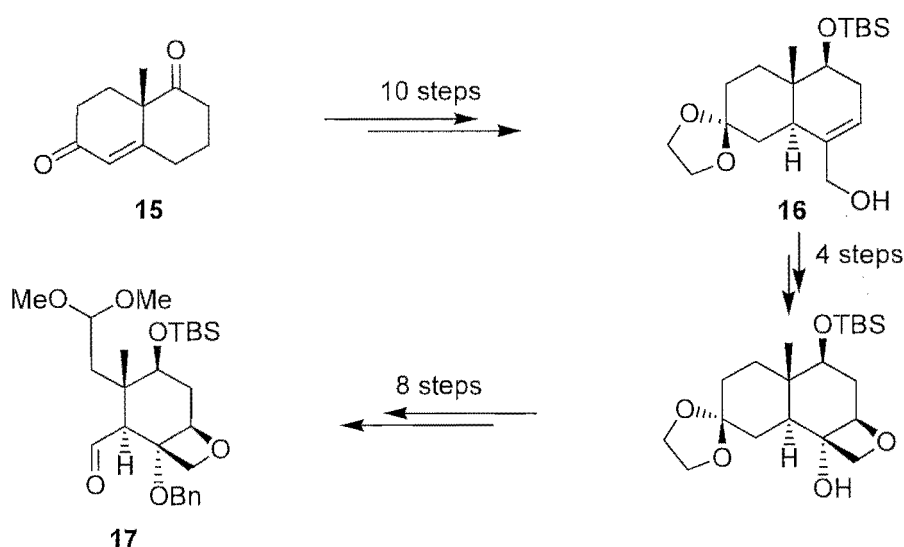


Figure 15 Danishefsky's synthesis of oxetane containing building blocks.

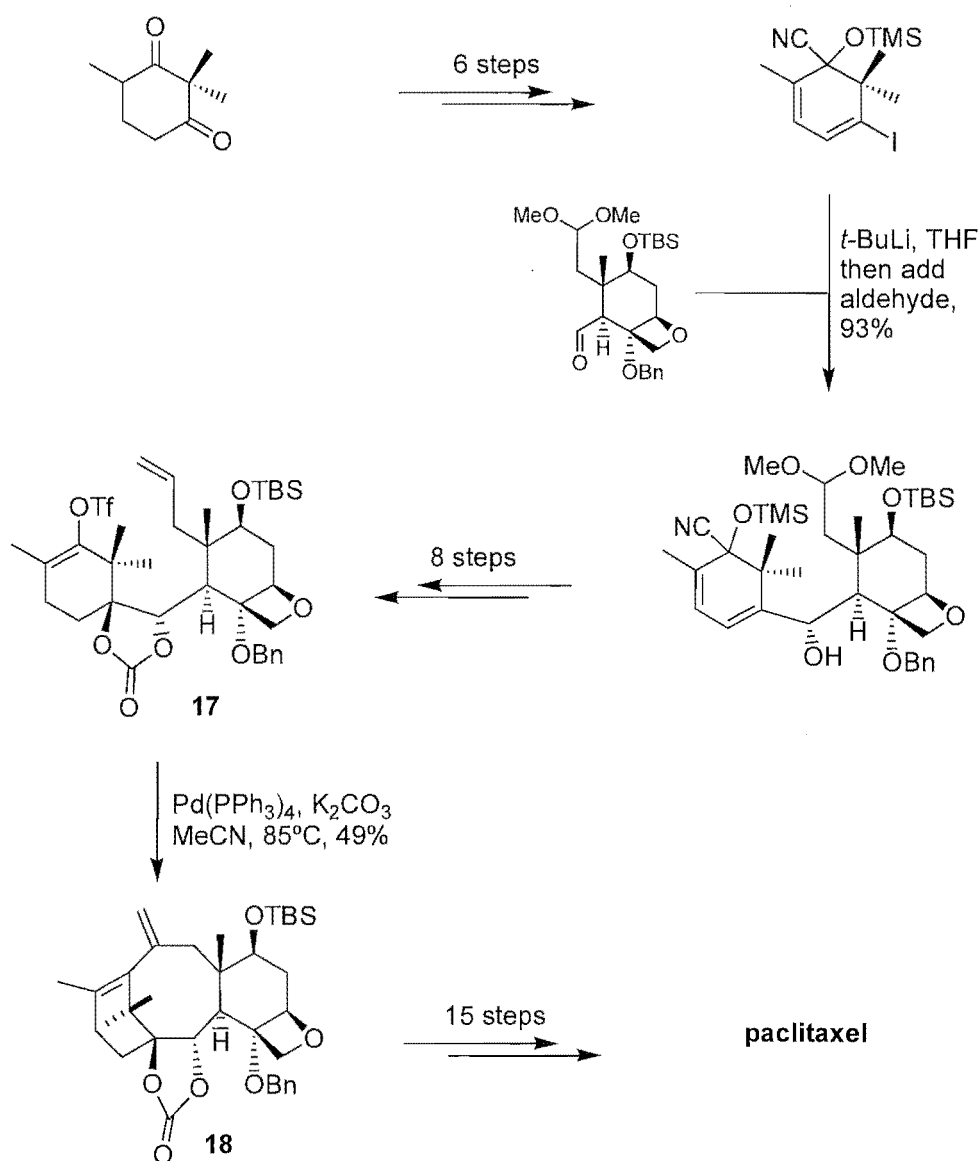


Figure 16 The Danishefsky synthesis of paclitaxel.

The synthesis reported by Danishefsky is an interesting example of the power of contemporary Pd-catalyzed chemistry. The choice of a Pd-catalyzed ring closure in such a setting was not without risk, especially given the effort expended in making the substrate. It allowed for the early installation of the oxetane and the correct level of oxidation in the C-ring. In this respect the Danishefsky synthesis yielded important information as many research groups had expected that the oxetane would be too sensitive to carry through a long sequence of reactions. If the problems involved in

removing the exocyclic methylene group formed by the Heck closure could be overcome and a shorter synthesis of the C-ring building block developed, the Danishefsky route may be able to provide access to interesting analogues.

1.3.5 Kuwajima (*rac*-Taxusin, 1996)

Kuwajima reported a second generation synthesis of taxusin in late 1996.³⁵ The synthetic strategy revolved around an intramolecular Mukaiyama-type cyclization that had been previously developed in the Kuwajima laboratories in earlier studies directed towards the synthesis of taxanes. As shown in **Figure 17** (see over page), the synthesis began with a C-ring precursor, onto which was attached an A-ring by Claisen condensation. Manipulation of this compound gave B-*seco* system **19** which contains the required acetal and a silyl enol ether. Treatment of this compound with trimethylaluminium triflate gave a tricyclic system with the correct C9/C10 *anti* stereochemistry. The angular C19 methyl group was installed by a cyclopropanation-reductive cleavage procedure that also removed the protecting groups. The resulting triol **20** was then subjected to the same transformations as those that completed the Holton synthesis.

Alongside the Danishefsky synthesis of paclitaxel, the route to taxusin reported by Kuwajima must stand as a benchmark. The synthesis is remarkably concise and is sufficiently flexible to allow the preparation of a number of the simpler taxanes.

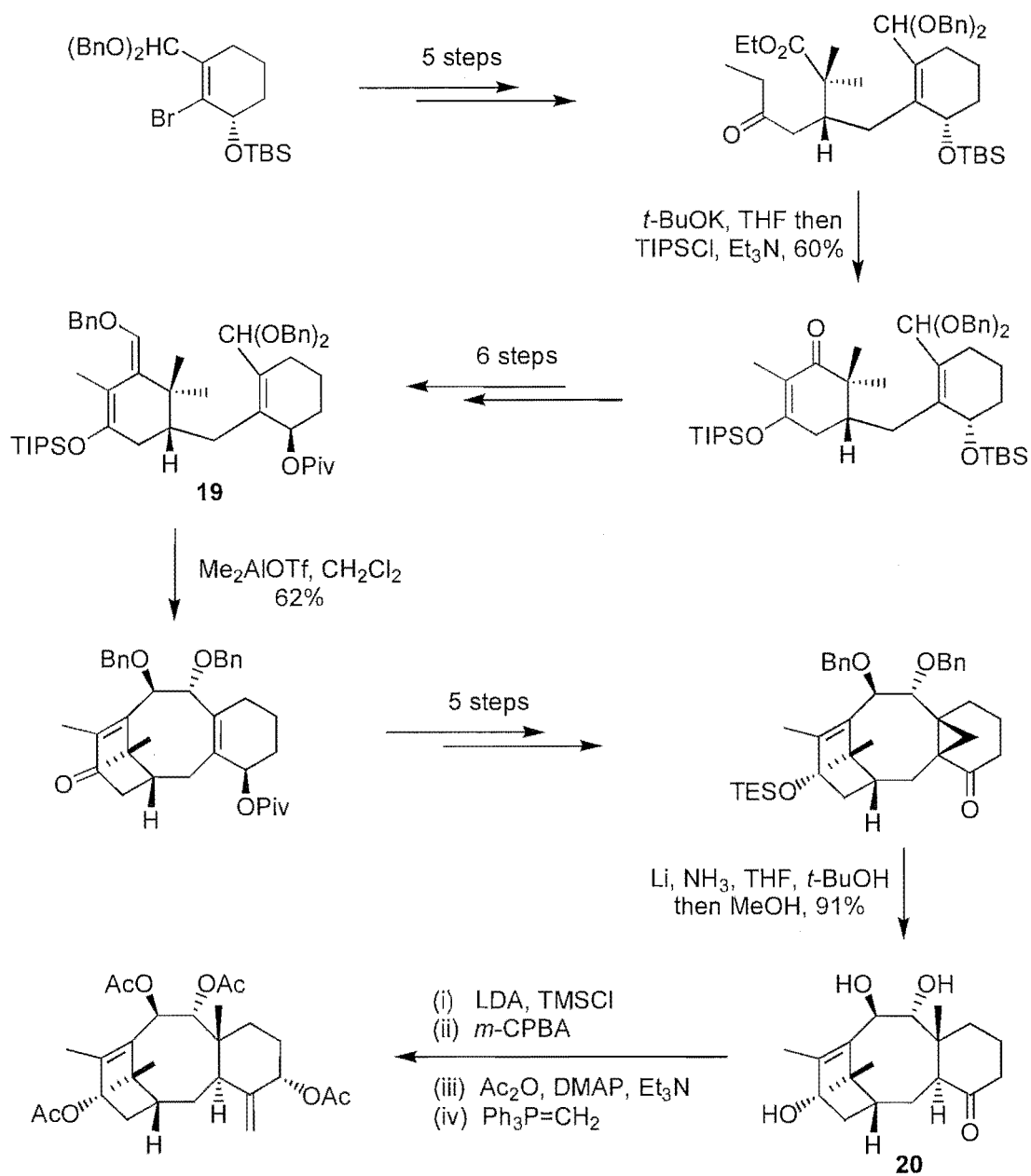


Figure 17 The Kuwajima synthesis of *rac*-taxusin.

1.3.6 Wender (Paclitaxel, 1997)

The Wender synthesis³⁶ was built on the seminal studies of diterpenoid isomerization and fragmentation by the groups of Whitham and Chretien-Bessiere in the late 1950s and 1960s.³⁷ Like Holton, Wender chose to overcome the problems involved in direct cyclizations to form eight-membered rings by employing a fragmentation of a tricyclic system. This approach was first reported with C-aryl taxanes in 1992 (**Figure 18**).³⁸

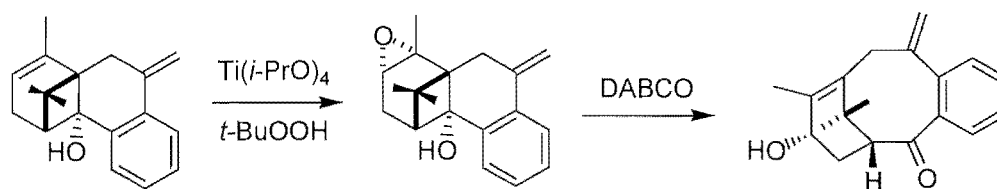


Figure 18 The Wender synthesis of C-aryl taxanes by fragmentation.

The paclitaxel synthesis began with (1*R*)-(+)-verbenone, the air-oxidation product of pinene (**Figure 19**, see over page). Alkylation, followed by several steps, allowed the preparation of bicyclic ynoate **21** which, upon treatment with lithium dimethylcuprate, underwent ring closure after conjugate addition of the methyl group. This ring closure solved a long-standing problem of Wender's 'Pinene Pathway' to the taxanes, namely the poor reactivity of a number of nucleophiles (and in particular enolates) towards this ketone. This compound could be readily manipulated *via* standard chemistry to give a substrate for the fragmentation chemistry. Treatment of the hydroxy-epoxide with DABCO resulted in fragmentation. The resulting compound was readily transformed into a fully functionalized AB-ring system **22**.

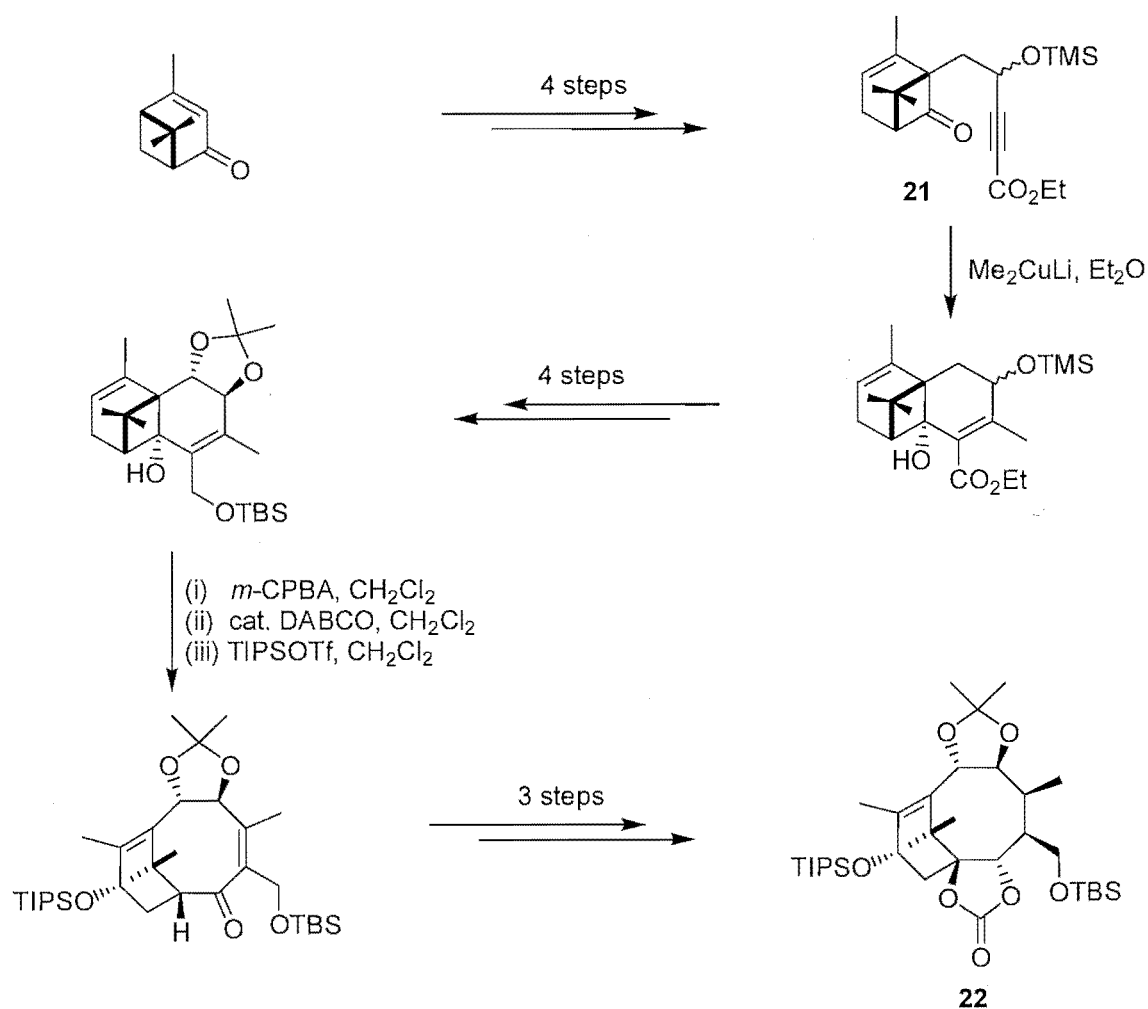


Figure 19 Wender's synthesis of the AB-ring structure *en route* to paclitaxel.

The C-ring was added by an intramolecular aldol closure (as shown in **Figure 20**, compounds **23** to **24**), a strategy predicated on the observation that paclitaxel undergoes epimerization at C7 – presumably *via* the intermediacy of a bicyclic ketoaldehyde. The tricyclic system obtained by this chemistry was advanced to paclitaxel by a number of steps, many of which were analogous to the previous paclitaxel syntheses.

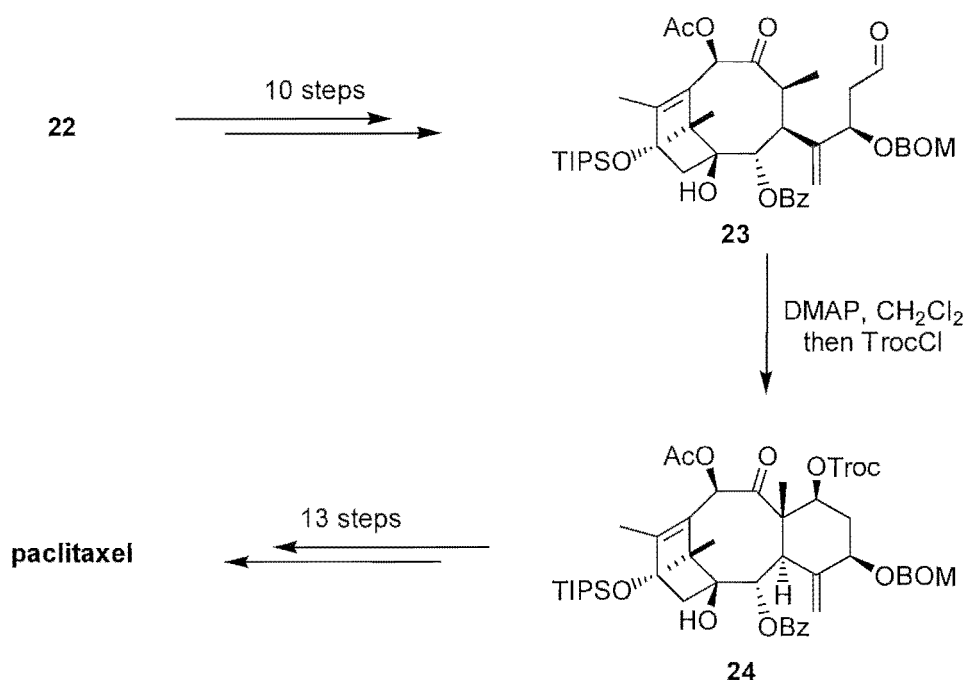


Figure 20 The formation of the C-ring by intramolecular aldol closure in the Wender synthesis of paclitaxel.

The Wender synthesis of paclitaxel is very efficient in its preparation of the AB-ring system. Unfortunately, the exocyclic hydroxymethyl group at C3 is a less than ideal functional group for the efficient annelation of the C-ring. The problems encountered here meant that the addition of the four carbons required for the C-ring required 14 steps. This aside, the synthesis does demonstrate some potential for the preparation and investigation of novel taxanes.

1.3.7 Mukaiyama (Paclitaxel, 1997)

After extensive reports on various aspects of taxane chemistry in both a total and partial synthesis context,³⁹ Mukaiyama's group reported a total synthesis of paclitaxel in late 1997.⁴⁰ The synthesis was based around the extensive use of aldol chemistry and began with neopentyl glycol (**Figure 21**). A long sequence involving several aldol reactions and a number of reduction-oxidation procedures gave α -bromo ketone **25**. This

compound, when treated with an excess of SmI_2 cyclized to give the central eight-membered ring in 70% yield. Elimination of the β -hydroxy group of the aldol adduct, followed by conjugate addition of a C-ring precursor, and intramolecular aldol reaction gave the AB-ring system **26**.

The A-ring was annelated by addition of homoallyllithium, followed by pyridinium dichromate oxidation and Wacker oxidation to afford diketone **27** (**Figure 22**). Intramolecular pinacol coupling of this compound occurred upon treatment with the low-valent titanium species generated by treatment of TiCl_3 with LiAlH_4 . A new method was employed to install a leaving group for oxetane formation (allylic oxidation of the exocyclic methylene with CuBr and PhCO_3Bu^t). However, the final steps of the Mukaiyama synthesis essentially followed the chemistry described by Holton and Nicolaou in their syntheses.

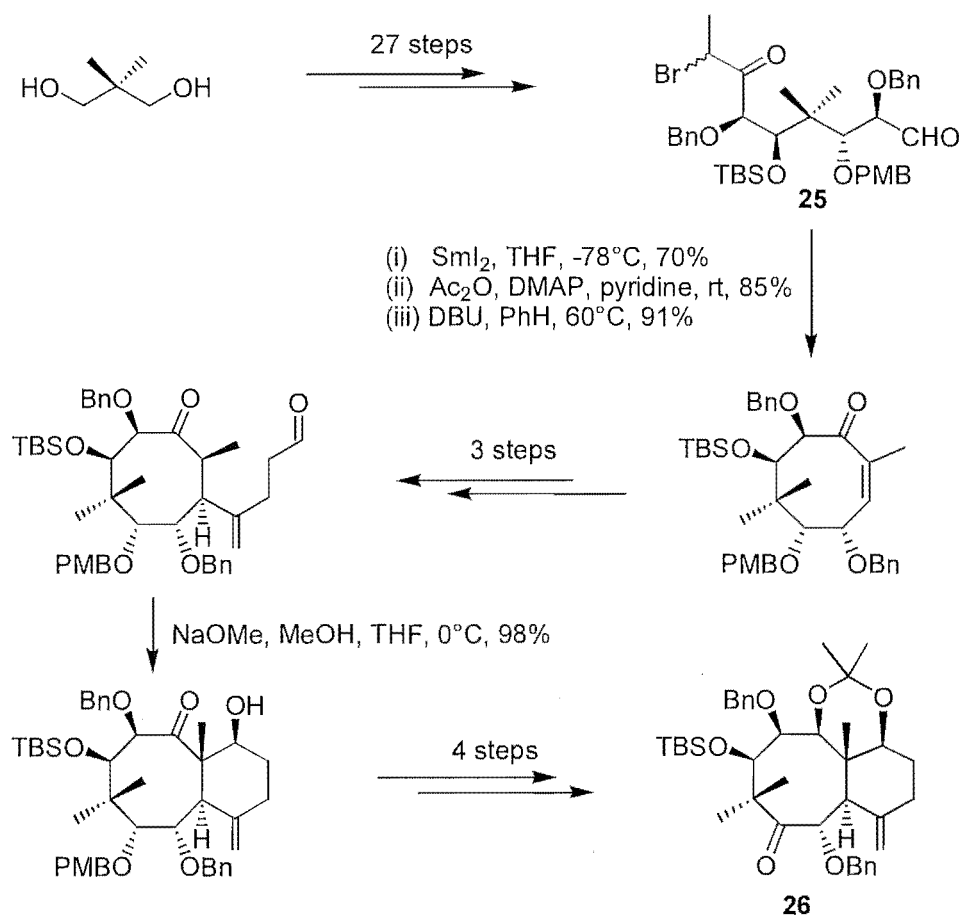


Figure 21 The initial stages of the Mukaiyama synthesis of paclitaxel.

The Mukaiyama synthesis differs from all of the other syntheses in that an A-ring is annelated onto a BC-ring structure late in the synthesis. This synthesis is the longest route to paclitaxel to date (60 steps), and is a clear example of the cost of extensive protecting group manipulation late in a synthesis. The long synthesis of the acyclic precursor to the B-ring will preclude the use of this route for further investigation. Nonetheless, the formation of the BC-ring structure by intramolecular aldol reaction is elegant and quite efficient and a substantial amount of information can be gleaned from a synthesis that is strategically so different from the others.

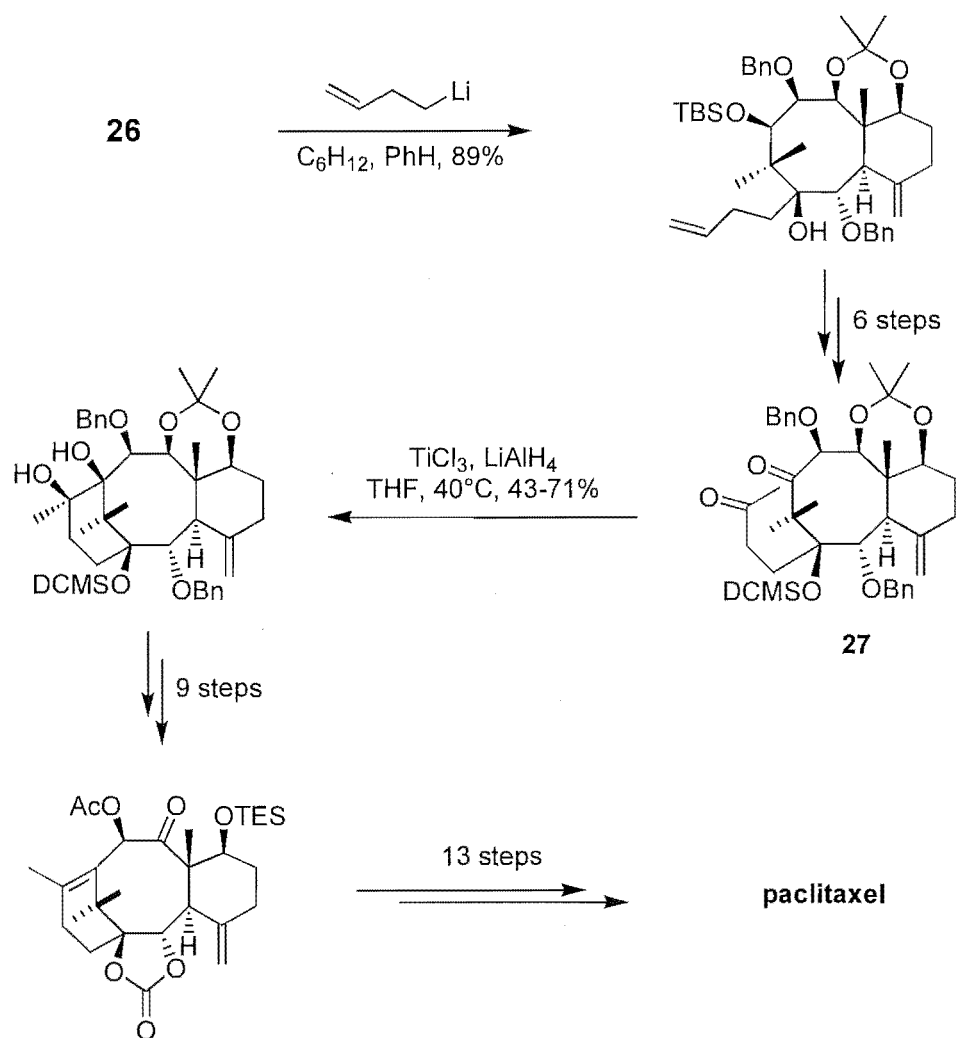


Figure 22 The Mukaiyama synthesis of paclitaxel.

1.3.8 Paquette (Taxusin, 1998)

The Paquette synthesis of taxusin was reported in mid-1998 and is based on the substantial contributions of this group in terms of the application of the oxy-Cope rearrangement to natural products synthesis.⁴¹ This strategy is based on earlier studies by Martin which had demonstrated the application of the anionic oxy-Cope rearrangement to the taxane ring system.⁴² The Paquette synthesis began with addition of a vinyl lithium compound to the camphor-derived ketone **28** (Figure 23). Anionic oxy-Cope rearrangement of the product gave tricyclic system **29** which contains the majority of the carbon framework of taxusin.

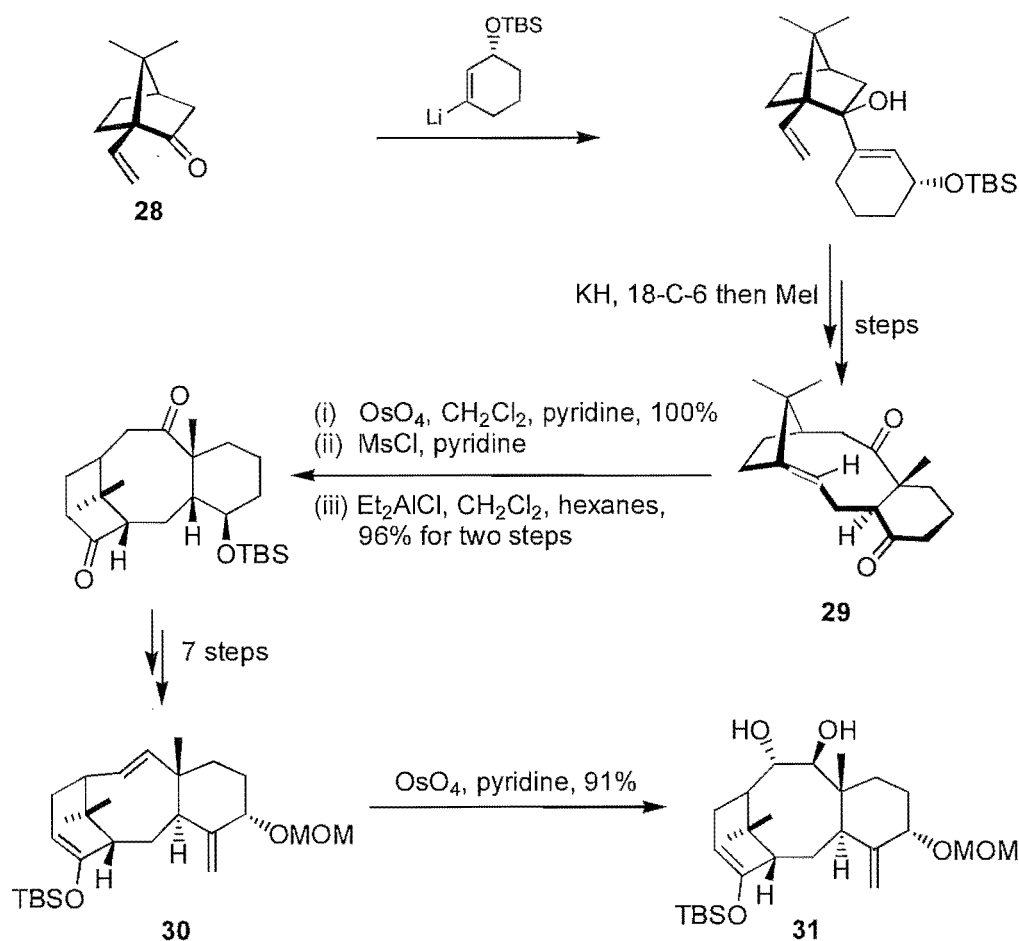


Figure 23 The Paquette synthesis of taxusin – the initial stages.

Further manipulation allowed the ring expansion of the five-membered ring to the required six-membered ring of taxusin. This compound was advanced to triene **30** which upon dihydroxylation surprisingly reacted only at the *trans*-disubstituted double bond and not the silyl-enol ether to give compound **31** which contains the required C9/C10 *anti* diol functionality. This compound was advanced to taxusin by a number of standard transformations, primarily involved in manoeuvring the A-ring ketone around the A-ring to facilitate installation of the double bond, C18 methyl group, and C13 hydroxy group (**Figure 24**).

Although longer than either of the two previous syntheses of taxusin, the Paquette synthesis of taxusin has added to our knowledge of possible transformations on the

taxane framework. Of particular note is the ability to install the C9/C10 diol system by dihydroxylation of an alkene precursor. Clearly, the synthesis was hampered by the problems involved in adjusting the position of the oxygenation in the A-ring and installation of the C18 methyl group and tetra-substituted alkene. If solutions can be found to these problems this route offers the potential of becoming an exceptionally concise route to taxanes such as taxusin.

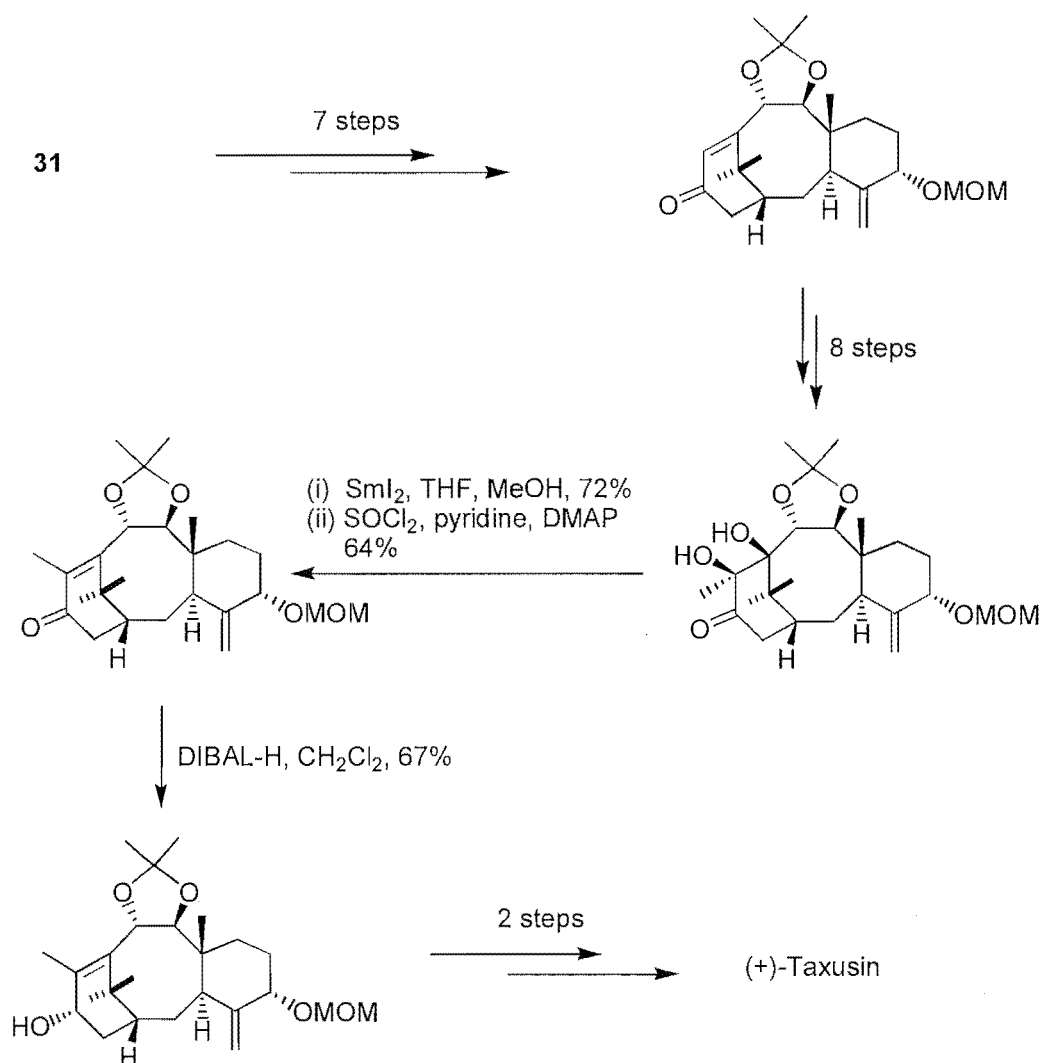


Figure 24 The final stages of Paquette's taxusin synthesis.

1.3.9 Kuwajima (Paclitaxel, 1998)

Armed with the knowledge gained during their synthesis of taxusin, Kuwajima's group reported a synthesis of paclitaxel in late 1998.⁴³ The same general strategy as that used for their taxusin synthesis was employed. The synthesis began by the addition of a C-ring precursor to enantiomerically pure hydroxy aldehyde **32** to give a diol that was protected as a cyclic boronate with trimethylboroxine (**Figure 25**). Like the other syntheses of paclitaxel that rely on closure at C9-C10, protection of the C1-C2 diol as part of a five-membered ring presumably provides some conformational restriction which aids cyclization. Exposure of this compound to dichlorobis(isopropoxy)titanium (IV) and subsequent removal of the boronate with pinacol gave the desired C9 α ,C10 β -tricyclic structure in good yield. This compound was advanced *via* a 14 step sequence to give cyclopropane **33**.

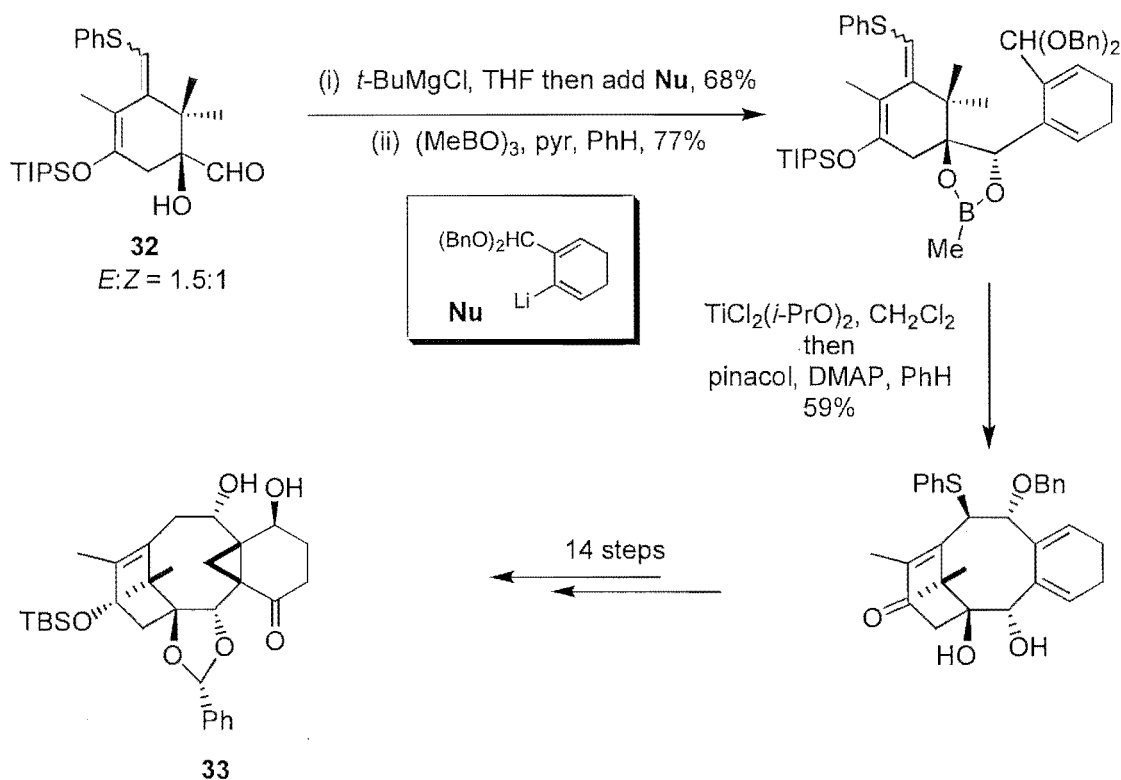


Figure 25 The initial stages of the Kuwajima paclitaxel synthesis.

Reductive cleavage of the cyclopropane and desilylation (**Figure 26**) gave a *ca* 1:1 mixture of stable enol **34** and the desired C3,C8-*trans* ketone **35**. Recycling **34** by treatment with sodium methoxide in methanol allowed a 65% overall yield of **35** to be obtained after repeating this procedure twice.

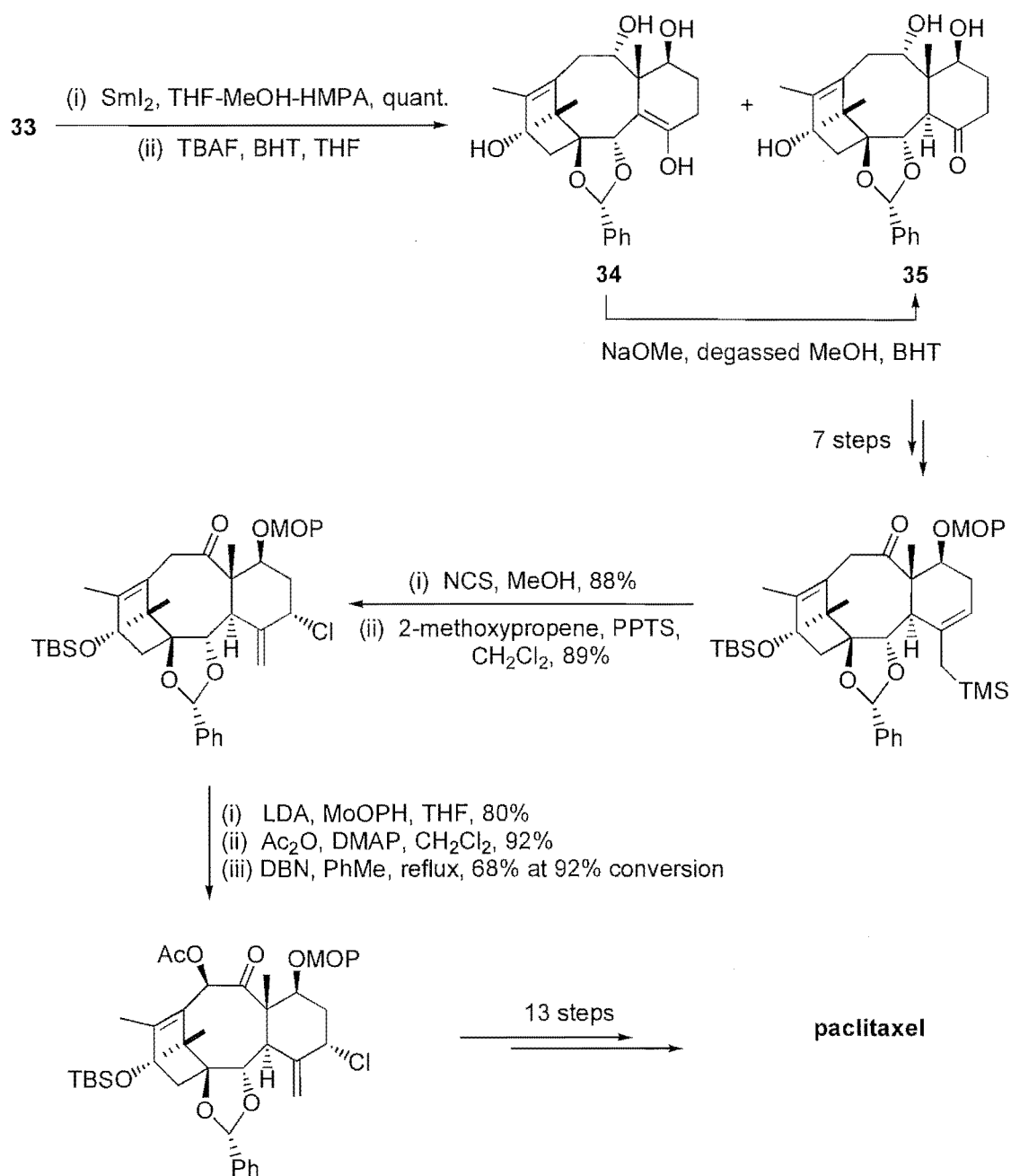


Figure 26 The closing stages of the Kuwajima paclitaxel synthesis.

Ketone **35** was advanced to an allylsilane which upon oxidation with *N*-chlorosuccinimide yielded the C5 α -chloride in good yield. Attempts to dihydroxylate the $\Delta^{4,20}$ -double bond with OsO₄ resulted in [unexpected] oxidation at the $\Delta^{11,12}$ -double bond. However, prior oxidation of C10 allowed a solution to this problem. Thus, treatment of the $\Delta^{9,10}$ -lithium enolate with MoO₅.pyr.HMPA gave the C10 α -alcohol, which, after acetylation, was readily epimerized to give the correct stereochemistry. Dihydroxylation of the $\Delta^{4,20}$ -double bond with OsO₄ now proceeded smoothly and allowed paclitaxel to be reached after a 13 step sequence that employed chemistry similar to the other syntheses of paclitaxel.

Although conceptually elegant, the Kuwajima synthesis of paclitaxel is very long (*ca* 55 steps). Like the Nicolaou and Mukaiyama syntheses, it is dominated by protecting group chemistry (eg, the C1,C2-diol was protected/deprotected seven times). Nonetheless, it possesses two very important features: (a) a C9,C10 ring closure method that can be employed on moderately functionalized substrates, without substantial protection, and *that proceeds in good yield*, and (b) that C10-oxygenation can be introduced late in the synthesis.

1.4 Significant Contributions

In addition to the groups having reported total syntheses, more than 50 groups worldwide have reported synthetic studies towards taxanes or taxane model systems. Much interesting chemistry has been developed and disclosed in this area. However, upon critical examination, very little of this chemistry has demonstrated realistic prospects for a total synthesis of any of the taxanes. Nonetheless, a number of strategies have been developed that either demonstrate possibilities for a total synthesis or have allowed the preparation of late-stage intermediates. The aim of this section is to give an overview of some of the more (in the author's opinion) significant contributions and also to outline the intramolecular Diels-Alder chemistry that has been reported in this area. It is not exhaustive and the reader is directed to more comprehensive reviews of the area.^{1,44}

1.4.1 Intramolecular Diels-Alder Approaches

1.4.1.1 Shea

The first reported example of an intramolecular Diels-Alder (IMDA) reaction applied to the taxanes came from the laboratories of Shea.⁴⁵ This work resulted in a concise synthetic route to C-aryl taxanes (**Figure 27**). The acyclic precursor was synthesized from substituted benzoic acid **36** and chlorodiene **37**, and treatment of this compound with diethylaluminum chloride resulted in smooth cyclization to the C-aryl taxane **38**, which exists exclusively as the *endo* atropisomer. An activation barrier of 27.1 kcal mol⁻¹ was established for the interconversion of the *exo* and *endo* atropisomers. This study illustrated the enormous potential of the IMDA reaction for the synthesis of the taxanes. However, there was insufficient functionality present on the substrate to allow facile synthesis of any of the naturally occurring taxanes.

Some efforts were made to synthesize more elaborate acyclic precursors in a related study (**Figure 28**).⁴⁶ However, cyclization of these systems gave rise to the C1 epimer of the natural taxanes. This problem remains unresolved.

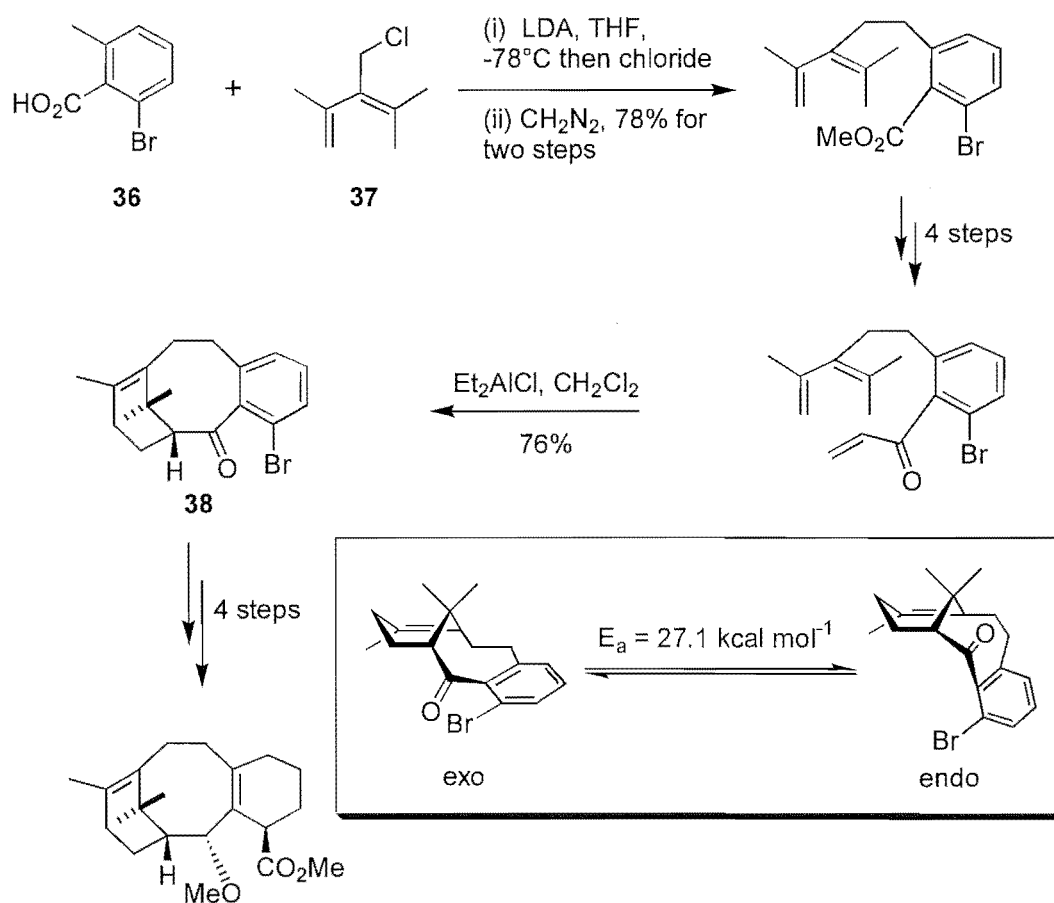


Figure 27 Shea's IMDA route to C-aryl taxanes.

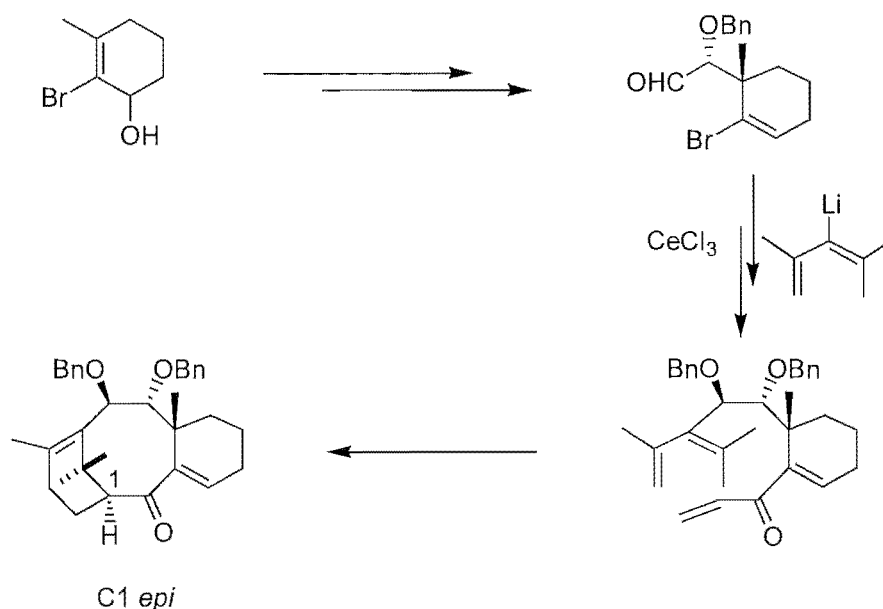


Figure 28 Shea's synthesis of C1 *epi*-taxanes by IMDA reaction.

1.4.1.2 Jenkins

Concurrent with the work of Shea, Jenkins also developed an IMDA route to the taxanes.⁴⁷ The required acyclic precursor was assembled from the Robinson annelation product of 2-methylcyclohexanone (compound **39**, **Figure 29**). Treatment of the acyclic IMDA precursor with boron trifluoride diethyl etherate gave the desired product. This result was the first example of a taxane IMDA reaction on a non-aromatic C-ring system and illustrates that the presence of the C19 methyl group does not affect the C1 stereochemistry in the product. However, as with Shea's original synthesis, there is insufficient functionality on the C-ring to allow a total synthesis to be entertained. Jenkins has recently reported a synthesis of enantiopure C-ring building blocks designed for incorporation into this route (**Figure 30**).⁴⁸

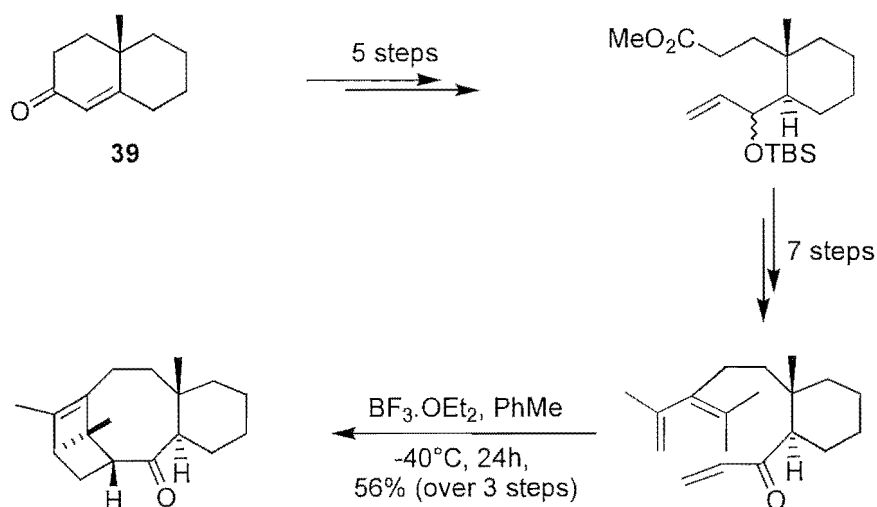


Figure 29 The Jenkins IMDA route to taxanes.

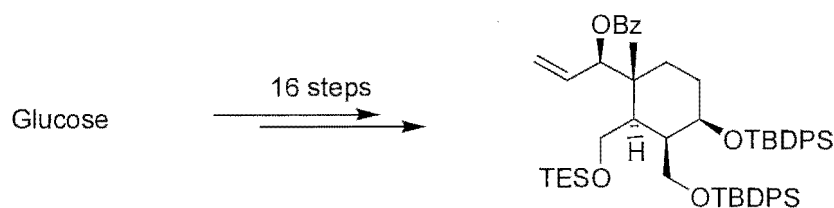


Figure 30 Jenkins' synthesis of enantiopure C-ring building blocks for IMDA reactions.

1.4.1.3 Danishefsky

As part of a large amount of work in the taxane area, the Danishefsky group have also investigated an intramolecular Diels-Alder approach to paclitaxel.⁴⁹ The majority of this work was conducted on steroid-taxane hybrids and led them to comment on the importance of the stereochemistry at C10 to both the rate and facial selectivity in IMDA reactions applied to the taxanes. As shown in **Figure 31**, the 10*R* diastereoisomer fails to give the desired taxane structure upon cyclization, whereas the 10*S* diastereoisomer undergoes cyclization to give the taxane ring system.

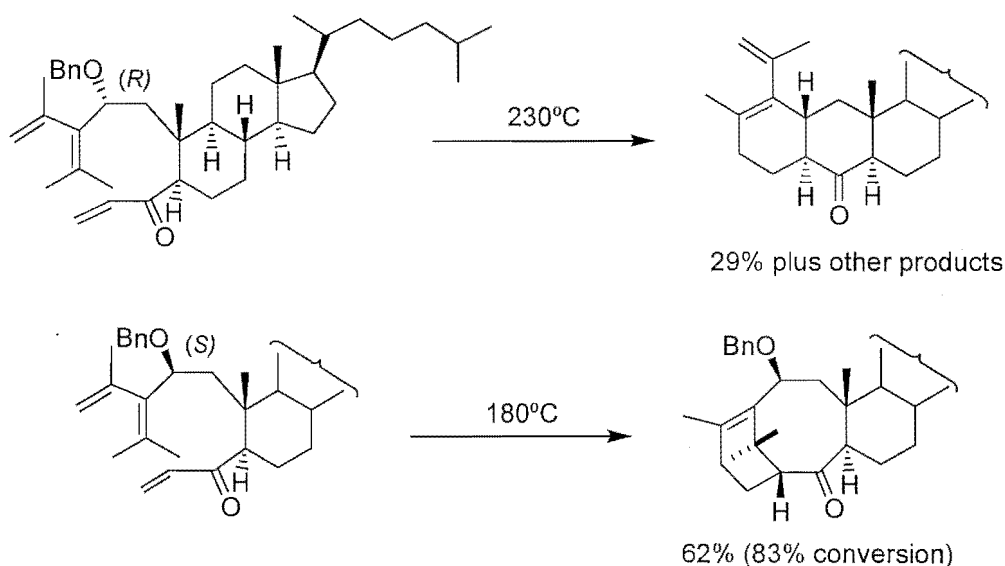


Figure 31 Danishefsky's studies on the application of IMDA reactions to taxane synthesis.

1.4.1.4 Winkler

The Winkler group has reported a number of approaches to the taxanes.⁵⁰ However, their most significant work has been in the exploration of sequential intramolecular Diels-Alder reactions to the taxane skeleton. A recent study outlined a concise route using this methodology to tricyclic structures and demonstrated some stereochemical features of the reaction when applied to the taxanes.⁵¹ Constructs with both *cis*- and *trans*-disubstituted C-rings are readily cyclized to give the requisite C1/C3 relative stereochemistry for the synthesis of taxanes (**Figure 32**).

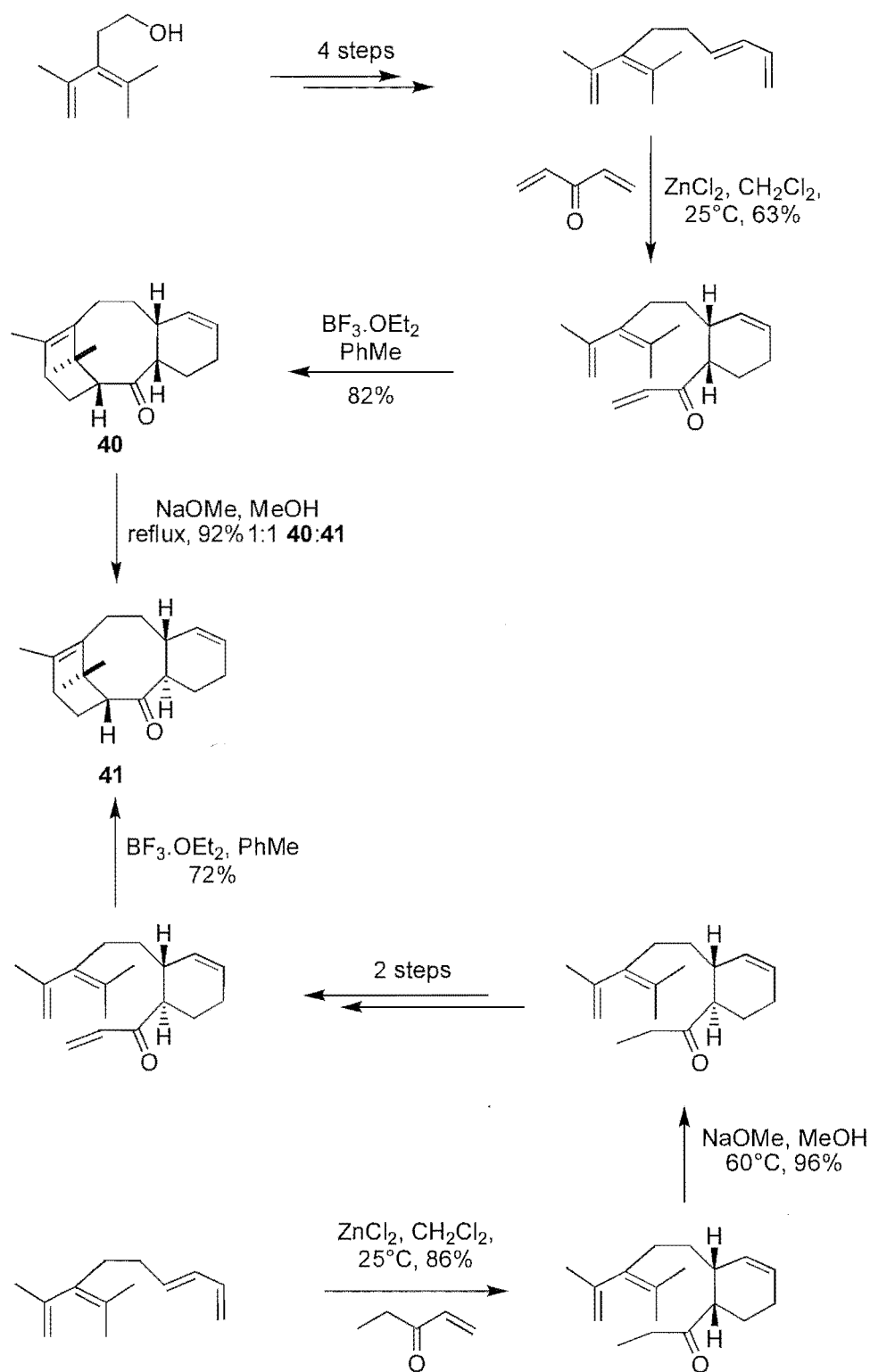


Figure 32 The Winkler sequential IMDA approach to the taxane skeleton.

Although very direct in its approach, this strategy will have to overcome a number of problems if it is to produce more functionalized substrates. Clearly, the installation of

further functionality on the C-ring, either before or after the IMDA reactions, will be expensive in terms of steps. It is also possible that more functionalized substrates may not yield the desired IMDA products (see for example the studies in this area by Shea and Danishefsky). Some of these issues have been addressed in related work which has produced a tricyclic structure with a bridgehead cyclopropane, which should be cleavable to give the desired C19 methyl group (**Figure 33**).⁵²

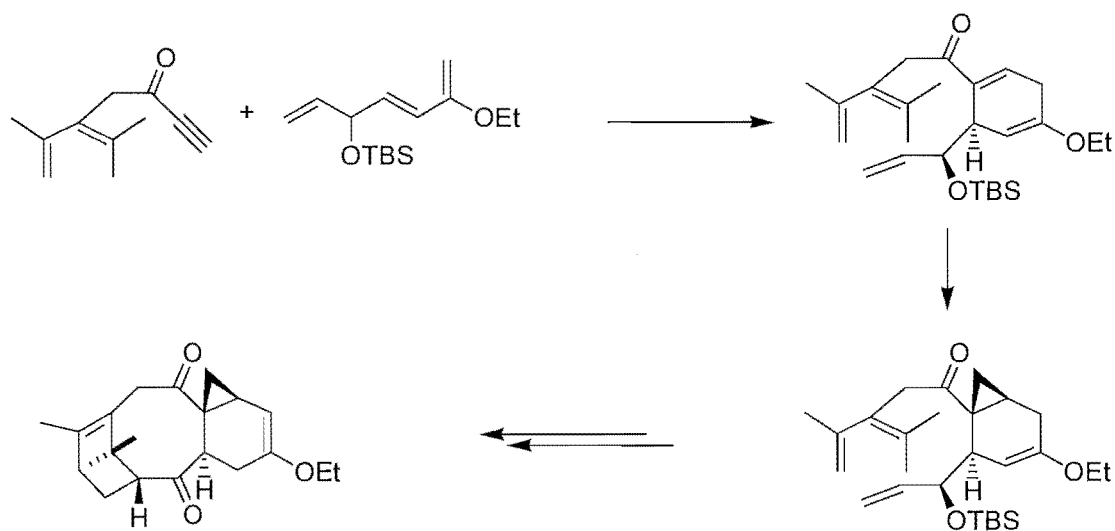


Figure 33 Winkler's IMDA approach to more functionalized systems containing cyclopropanes.

1.4.1.5 Sakan

The group of Sakan was the first to report a C-ring intramolecular Diels-Alder approach to the taxanes.⁵³ In this study, an acyclic precursor containing a two carbon bridge in the A-ring was prepared by a sequence starting with known enone **42** (**Figure 34**). When the IMDA substrate was heated to 160°C, the desired tricyclic system **43** was formed in 70% yield. Surprisingly, when Lewis acids were used to promote the cyclization, the C8 epimer **44** was formed as the predominant product. Whilst Lewis acids are well known to enhance *endo* selectivity, the reversal of selectivity observed here is unusual. The two epimers presumably arise from *exo* and *endo* transition states respectively.

Although some challenges are presented by this route – for example, the development of a cleavable A-ring bridge – this is a very promising approach to taxane synthesis. Unfortunately, these studies have not been continued due to the untimely death of Sakan in 1984.

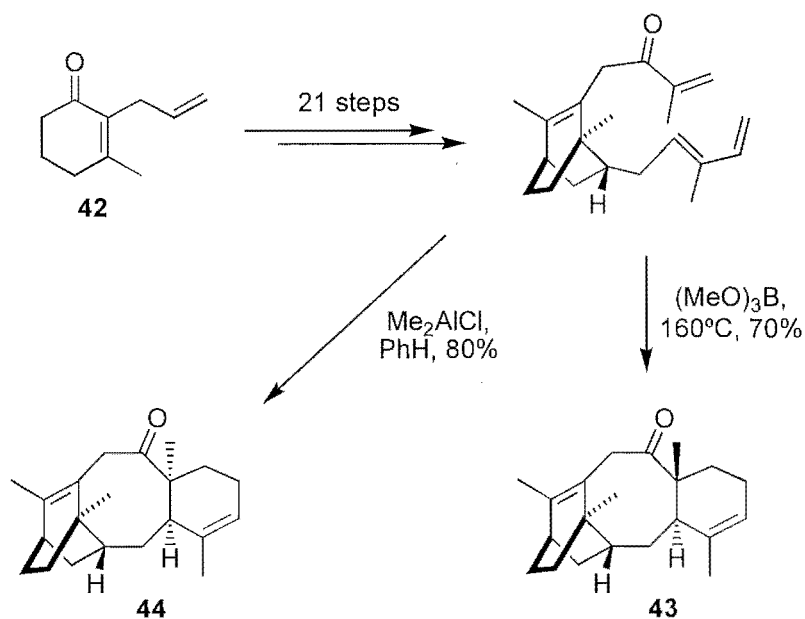


Figure 34 Sakan's C-ring IMDA approach to the taxanes.

1.4.1.6 Fallis

A number of groups have reported C-ring IMDA approaches based on the original report of Sakan. One of the furthest advanced is Fallis' group, who have reported extensive studies on routes to IMDA substrates and also a completed synthesis of an ABC tricyclic structure (**Figure 35**).⁵⁴

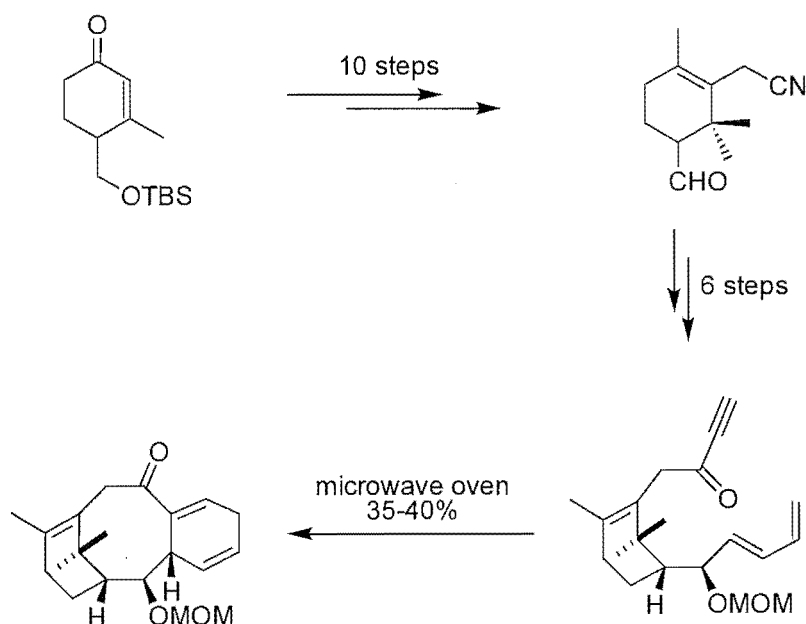


Figure 35 The Fallis approach to taxane synthesis by C-ring IMDA reaction.

1.4.2 The Magnus Pinacol Rearrangement/Expansion Strategy

The Magnus group has reported a significant amount of work in the taxane area.^{55,56} In their most advanced contribution, an advanced tricyclic structure was assembled by a route that was both novel and elegant.⁵⁶ As shown in **Figure 36**, a system containing a seven-membered ring attached to a C-ring **45** was assembled by an intramolecular pyrylium ylide – alkene cyclization. The seven-membered ring could be expanded by addition and cleavage of a cyclopropane, also allowing for the installation of the *gem*-dimethyl group. Further transformations allowed compound **46** to be prepared. Treatment of this compound with lithium hexamethyldisilylamide and then dissolving metal conditions resulted in ring closure to form the A-ring (**Figure 37**). Elimination of the oxido bridge and installation of the C18 methyl group gave an advanced intermediate from which it seems possible to reach paclitaxel. A recent report has dealt with the installation of the C1 hydroxy group⁵⁷ but several questions remain unanswered, including the isomerization of the $\Delta^{12,13}$ double bond to the correct position ($\Delta^{12,12}$).

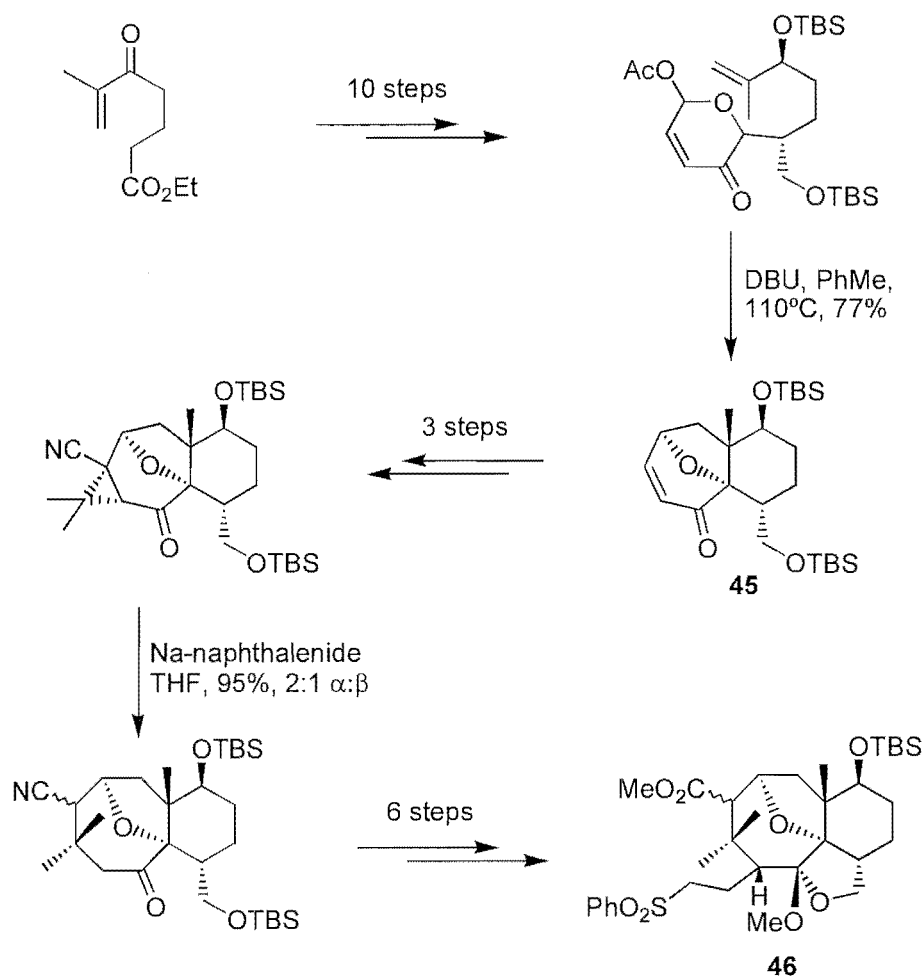


Figure 36 The Magnus synthesis of paclitaxel intermediates by intramolecular pyrylium ylide – alkene cyclization and ring-expansion.

Although an interesting approach, the Magnus route to taxanes at present is hampered by its length. If more efficient ways of installing the A-ring (including regiospecific placement of the double bond) and various oxygens can be found, then this route may become more competitive with the other strategies employed for the total synthesis of paclitaxel and taxusin.

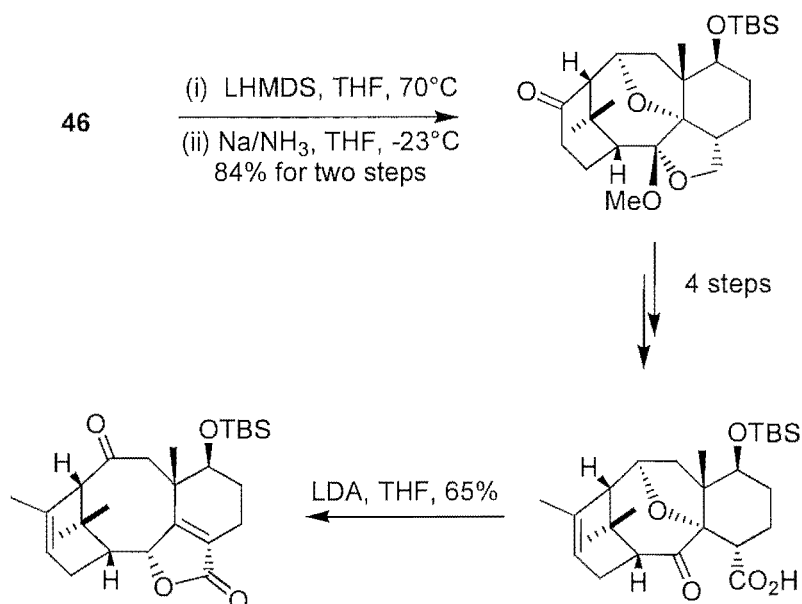


Figure 37 Formation of the A-ring and cleavage of the oxido bridge in Magnus' synthesis of paclitaxel intermediates.

1.4.3 Acyclic Ring Closure Approaches

1.4.3.1 Kishi

The Kishi group has reported an approach to the taxanes based on the intramolecular Ni^{II}/Cr^{II} – mediated coupling of vinyl halides and alkenes that has been extensively utilized in their laboratories. A *B-seco* system **46** was assembled by coupling of a vinyl lithium A-ring precursor with a C-ring aldehyde (**Figure 38**).⁵⁸ This compound was advanced to vinyl iodide **47**, which smoothly cyclized (albeit very slowly) over a period of two days upon treatment with CrCl₂ containing 1% NiCl₂. Although strategically very similar to both the Danishefsky and Nicolaou syntheses, this route may be able to produce paclitaxel or analogues in a concise fashion as it should be possible to perform the coupling on heavily functionalized substrates. Unlike the Danishefsky synthesis, it does not face the problem of removing an exocyclic methylene group after ring closure.

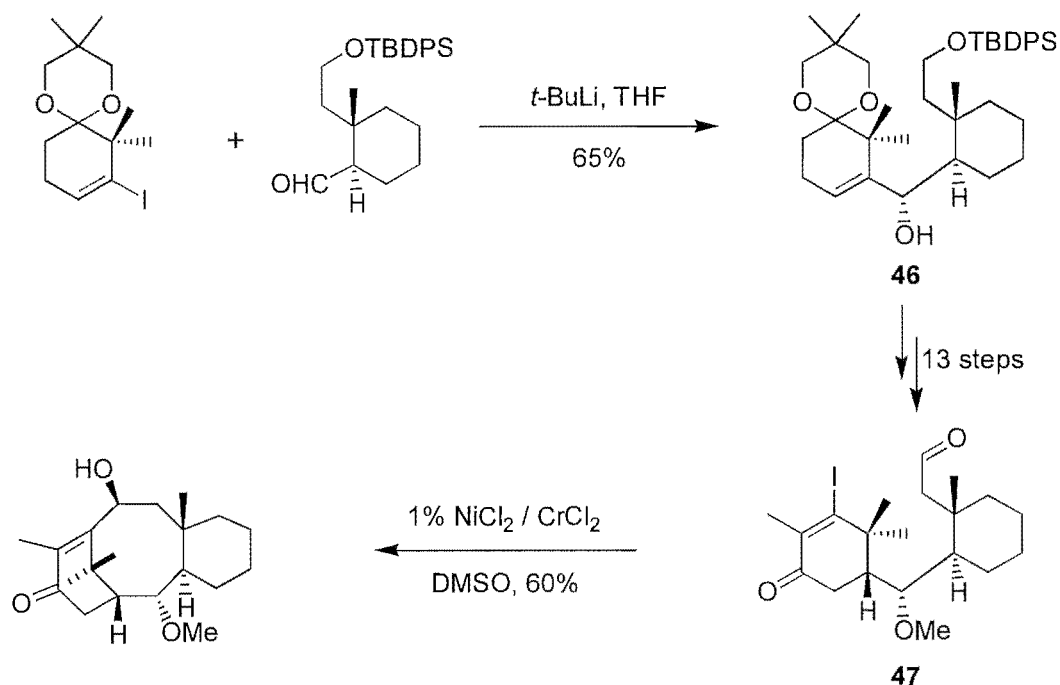


Figure 38 Kishi's $\text{NiCl}_2/\text{CrCl}_2$ mediated synthesis of the taxane skeleton.

1.4.3.2 Stork

Stork has recently disclosed a strategy directed towards the synthesis of paclitaxel that is conceptually similar to the Nicolaou and Danishefsky syntheses. The strategy requires formation of the B-ring by closure of a *seco* precursor at the C9-C10 position. Stork's solution to this problem is to form the bond by alkylation of a cyanohydrin.⁵⁹ As shown in **Figure 39** the A-ring precursor **48** (synthesized from methyl geranate) is coupled with aldehyde **49**. Esterification and Ireland-Claisen rearrangement of the alcohol gave the aldehyde acetate **50**. Treatment of compound **50** with potassium cyanide, then acetalization and conversion of the acetate to a halide allowed cyclization to form the AB-ring system. Extension of the allylic alcohol by Johnson-Claisen rearrangement and intramolecular aldol closure gave a tricyclic ring system that differs from paclitaxel only in its level of oxidation.

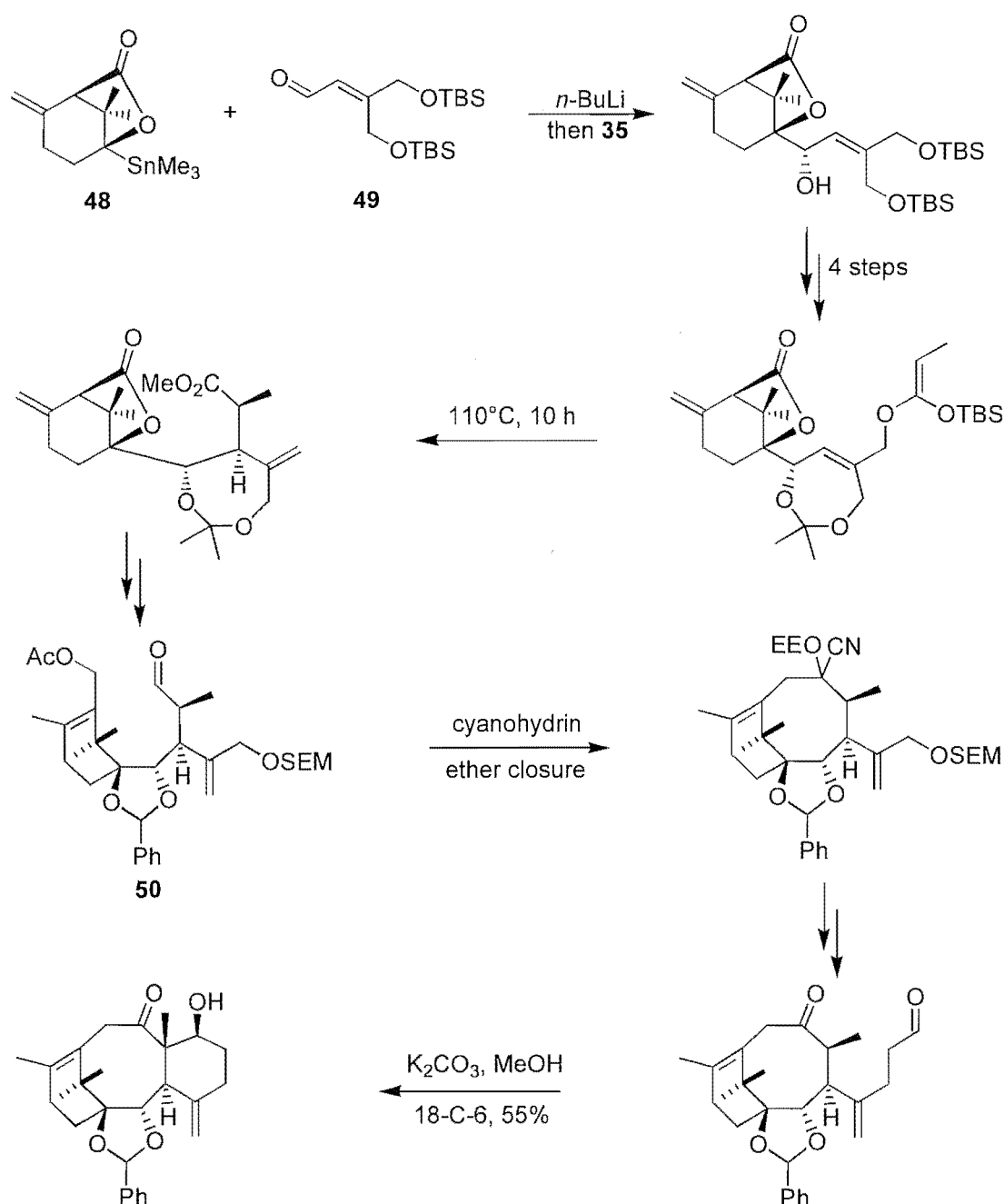


Figure 39 Stork's approach to the synthesis of paclitaxel.

The Stork strategy for the synthesis of paclitaxel, like a number of other routes, has the potential to provide a concise synthetic route to the taxanes. Although much of the chemistry required to convert their most advanced compound into paclitaxel has been described in the total syntheses, there are some remaining problems. For example, as part of degradative studies, Nicolaou has noted that benzylidene acetals of the C1-C2

diol system cannot be removed.⁶⁰ This led to their selection of the cyclic carbonate that has seen wide use both as a protecting group and as a precursor to the C2 benzoate. However, the recent synthesis of paclitaxel by Kuwajima has indicated that this may be very substrate dependent (see **Section 1.3.9**).

1.5 Work Described in this Thesis

The overview provided in **Sections 1.3** and **1.4** has illustrated that a large number of strategies for taxane synthesis have been investigated. Some have proved fruitful in terms of total syntheses, whereas others have yet to progress past the point of model studies. It seems important to the author that any synthetic studies on the taxanes should meet several aims:

- (1) Ideally, any new strategies for taxane synthesis need to be more concise than those currently known. Another protracted synthesis would be unlikely to advance knowledge in the area.
- (2) A synthesis should be sufficiently flexible or modular to allow modification for the preparation of analogues. Although much work has been reported on paclitaxel analogues this work has focussed on variation in the acyl groups and not on the carbocyclic skeleton.
- (3) From an academic point of view, it is important that the synthesis should—within the constraints imposed by 1 and 2 above—allow for the exploration and development of new chemistry.

With these points in mind, an overview of the strategy for taxane synthesis described in this thesis is illustrated below (**Figure 40**). Taxinine was chosen as the target compound as it was viewed as an ideal vehicle for the exploration of the ideas outlined

in **Figure 40**. It has the advantages of being somewhat decreased in complexity compared with paclitaxel, and also it has generated little synthetic interest.

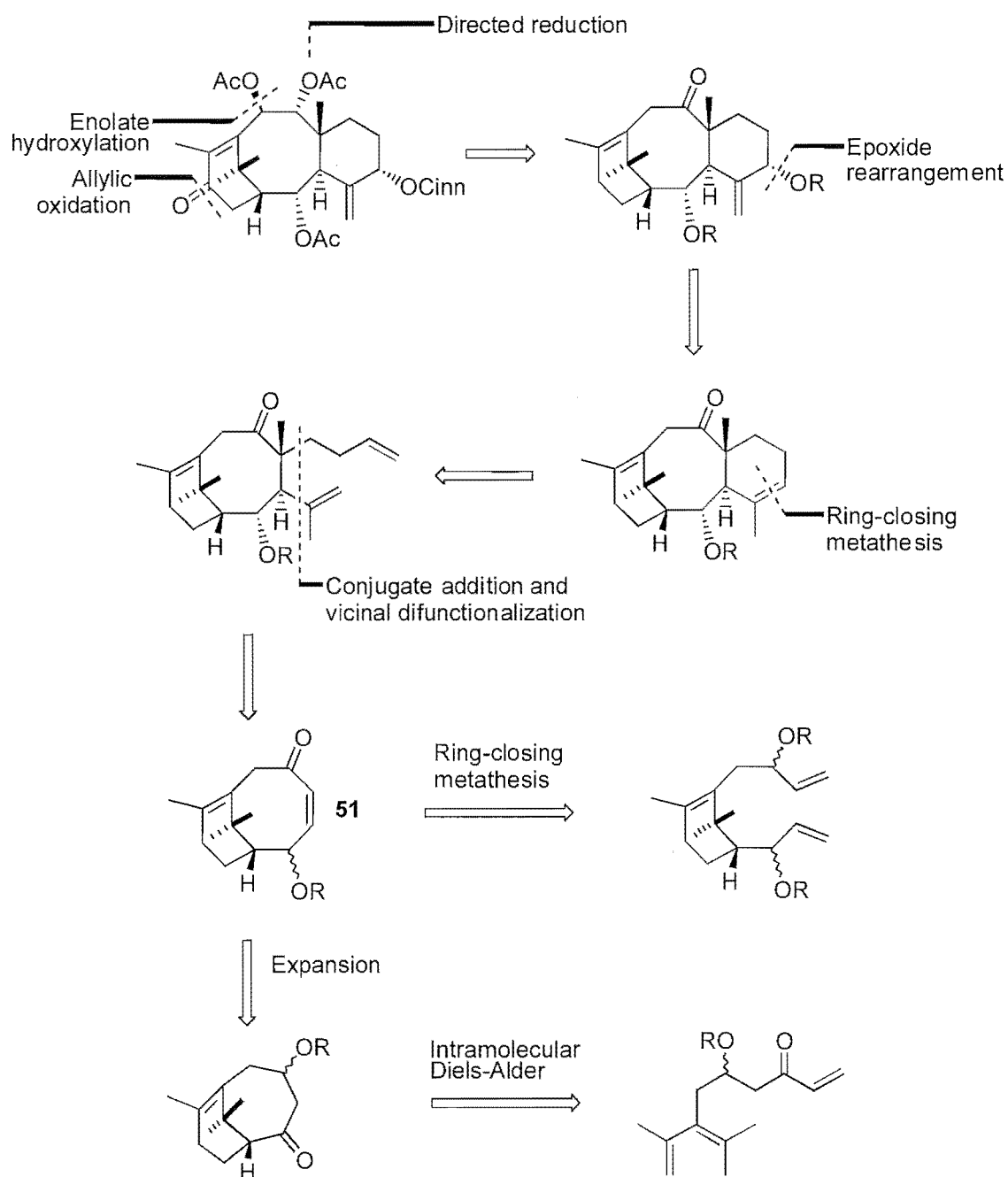


Figure 40 A strategic overview of the author's thinking on taxane synthesis. R is used to denote a generic protecting group.

As can be seen, the crucial compound is a bicyclic enone of general type **51**. It is thought that compound of this type will contain all of the necessary functionality to allow the completion of a synthesis. Based on the X-ray structures of a number of taxanes the likely shape of this compound is expected to be as shown in **Figure 41**. If correct, this would also mean that sufficient stereochemical information is contained in compounds of this type to allow introduction of the remaining functionality with control of stereochemistry.

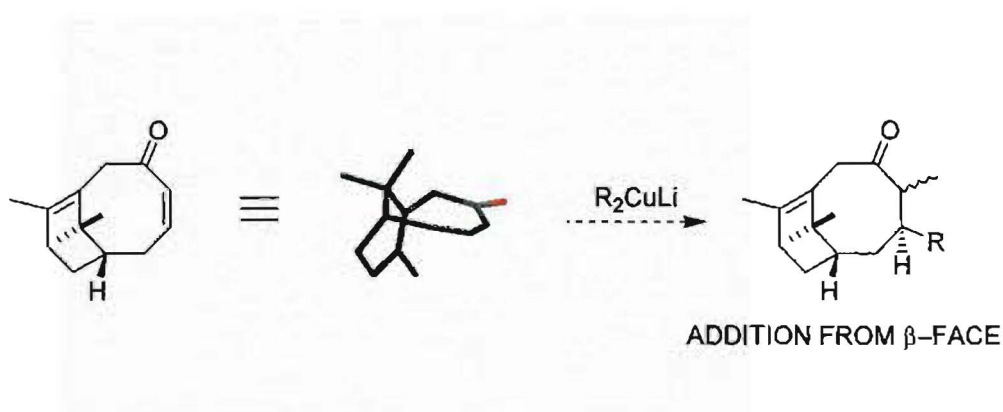


Figure 41 Addition of nucleophiles to the *exo* face of bicyclic enones. The presence of a protected C1 α -hydroxy group could be expected to further favor addition as shown.

A number of significant questions relating to likely functional group manipulations in the closing stages of the synthesis were unanswered at the outset of this work. However, the recent synthesis of paclitaxel by Kuwajima answered some of these issues (eg, the possibility of introduction of the C10-oxygenation from a $\Delta^{9,10}$ enolate).

The initial aim of the research was to access A-ring building blocks. This work is described in **Chapter Two**. The use of these building blocks in the synthesis of substrates for an unsuccessful approach to the taxane AB-ring system by ring-closing metathesis is described in **Chapter Three**. An alternative approach to the AB-ring system is described in **Chapter Four**. This approach allowed the synthesis of a

bicyclo[4.3.1]decene system. Preliminary efforts to ring-expand this compound are also described. A model study to explore some aspects of the end-game strategy described in **Figure 40** is delineated in **Chapter Five**. This study has demonstrated the application of ring-closing metathesis as a potential method for the annelation of the C-ring. The future potential of the chemistry described in this thesis is outlined in **Chapter Six**.

Chapter Two

The Synthesis of A-Ring Building Blocks

2.1 Introduction

The initial goal of the research described in this thesis was the synthesis of A-ring building blocks. These compounds, and the intermediates used in their synthesis, were expected to form key starting points for the strategies described in **Chapter 3** and **Chapter 4** (Figure 2.1).

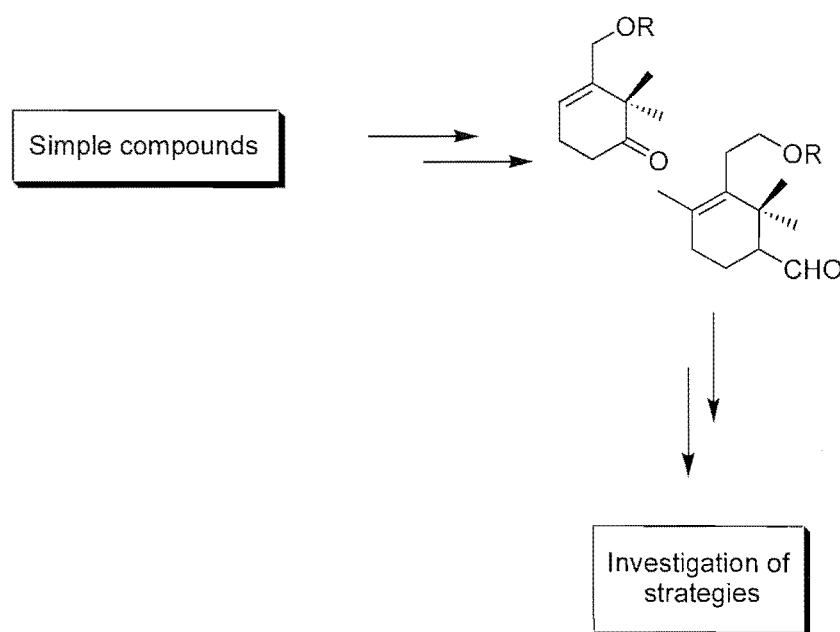


Figure 2.1 The synthesis of A-ring compounds as a starting point for further investigations. R is used to indicate a generic protecting group.

The strategic importance of A-ring building blocks to a number of reported strategies has resulted in a significant amount of work directed towards developing routes to these compounds. The major synthetic challenges posed by a fully functionalized (bar the C13 side chain) paclitaxel A-ring substructure are: (1) oxygenation at C13 (taxane numbering), (2) the *gem*-dimethyl group, (3) the regiospecific installation of the $\Delta^{11,12}$ double bond, and (4) provision for attachment of further functionality at C1 or C2. This is schematically presented in **Figure 2.2**.

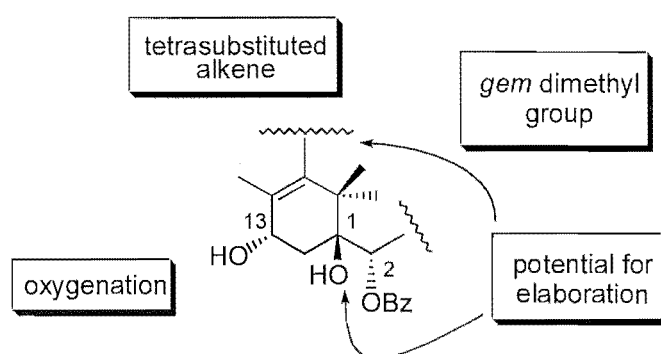


Figure 2.2 Issues to be addressed in the synthesis of a fully functionalized paclitaxel A-ring substructure

These problems have been addressed in a number of different ways. Some illustrative examples—which are by no means exhaustive—are presented below.⁶¹

In an early approach to the synthesis of an A-ring, Frejd and co-workers employed a Lewis acid promoted cyclization to make the cyclohexane ring (**Figure 2.3**).⁶² This approach addresses all four of the strategic issues above, and is also stereoselective. However, it also illustrates that the installation of stereochemistry can be an expensive process when measured in terms of steps. It is now known from other approaches to the A-ring, and also from the total syntheses, that it is possible to delay the installation of

the stereogenic centers until later in the synthesis. For example, several of the total syntheses install the C13 stereogenic center late in the synthesis by reduction of C13 ketone from the more exposed β face of the A-ring (**Figure 2.4**).

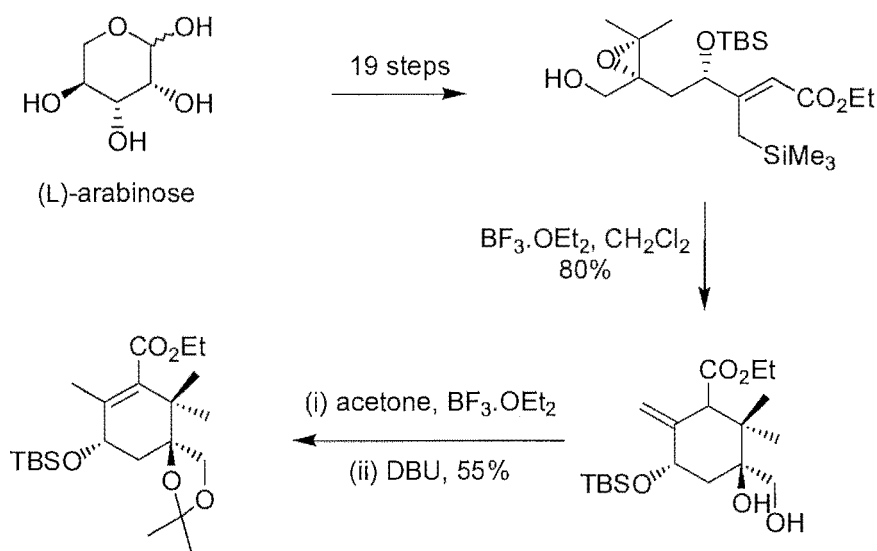


Figure 2.3 Frejd and co-workers' synthesis of a fully functionalized paclitaxel A-ring.

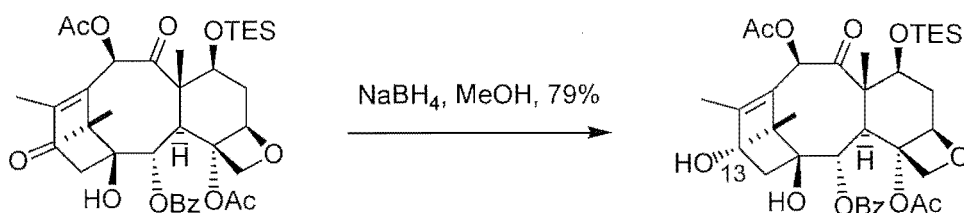


Figure 2.4 Stereoselective installation of the C13 alcohol from the more exposed β face late in the Danishefsky synthesis of paclitaxel.

Nicolaou's group has utilized the Diels–Alder reaction to assemble the A-ring (**Figure 2.5**).⁶³ This strategy allows for the regiospecific placement of the double bond and the *gem*-dimethyl group. The opportunity for further elaboration at C1 is provided by a ketone and the issue of C13-oxygenation is dealt with by regioselective allylic oxidation.

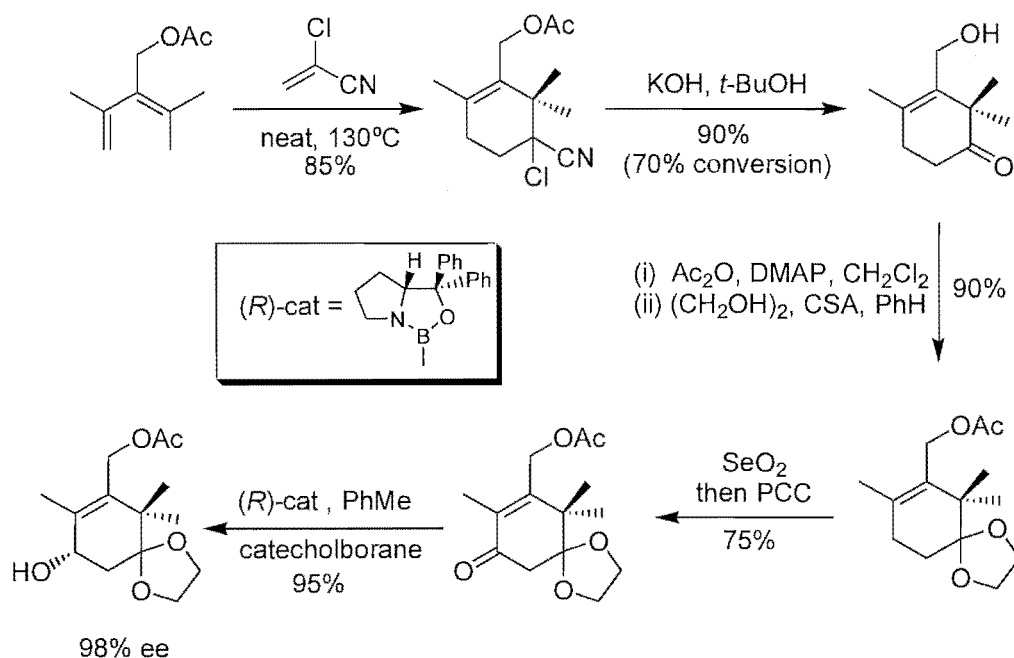


Figure 2.5 The Nicolaou synthesis of advanced precursors to the paclitaxel A-ring.

Danishefsky and co-workers have described a similar approach to that of Nicolaou (**Figure 2.6**).⁶⁴ The chemistry employed does not directly install the $\Delta^{11,12}$ double bond, but investigation has shown the versatility of a C11 ketone as a precursor to various functionality (such as vinyl triflates and halides) at this position. In the context of their total synthesis, this proved important as the eight-membered B-ring was formed by reaction of such a vinyl triflate with an alkene under Pd(0) catalysis. The C13-oxygenation—as with Nicolaou’s approach—was introduced by allylic oxidation.

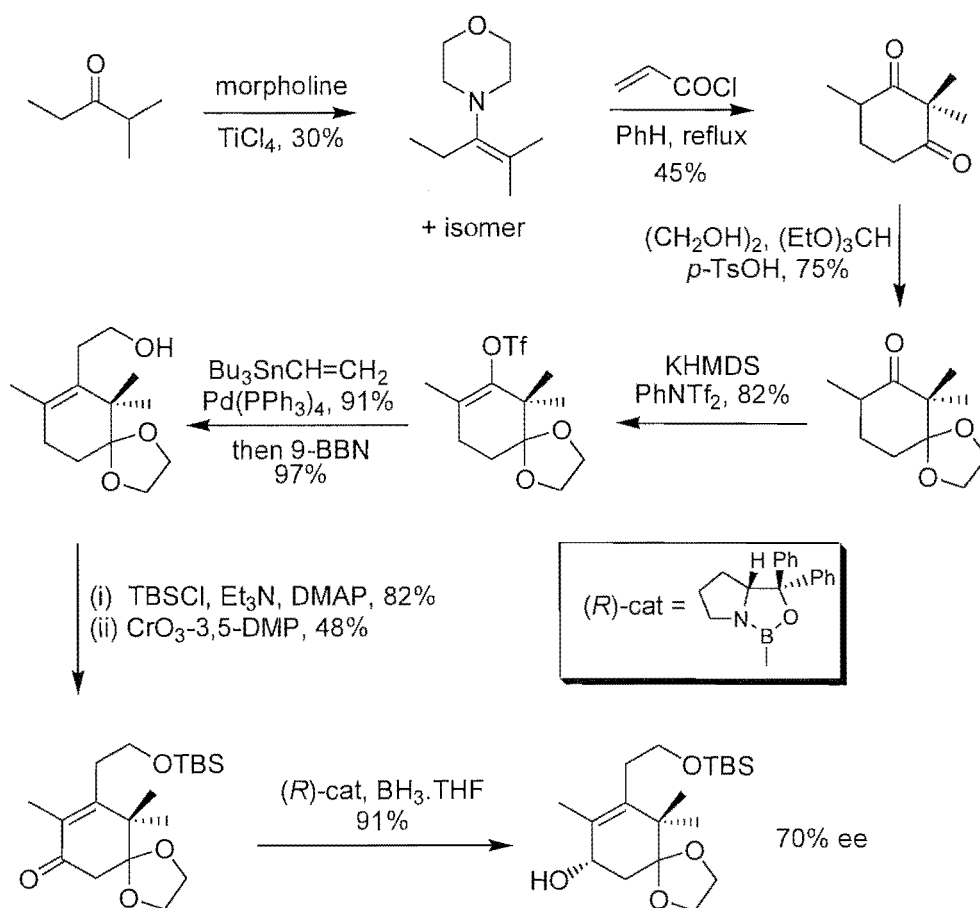


Figure 2.6 The Danishefsky synthesis of advanced precursors to the paclitaxel A-ring.

Fallis and co-workers have reported a number of approaches to the taxane A-ring.⁶⁵ One of their routes, beginning with β -ionone, is shown in **Figure 2.7**. With the *gem*-dimethyl group and tetrasubstituted double bond available in the starting material, the major issues to be addressed in this approach are C13-oxygenation and the potential for elaboration at C1/C2. The problem of C13-oxygenation is solved by the same allylic oxidation – reduction approach as Nicolaou and Danishefsky. Potential for elaboration at C1/C2 is obtained after a number of transformations involving addition of two carbons (*via* conjugate addition of vinylmagnesium bromide) followed by oxidative removal of one, or both, of these carbons to leave either an aldehyde or a ketone.

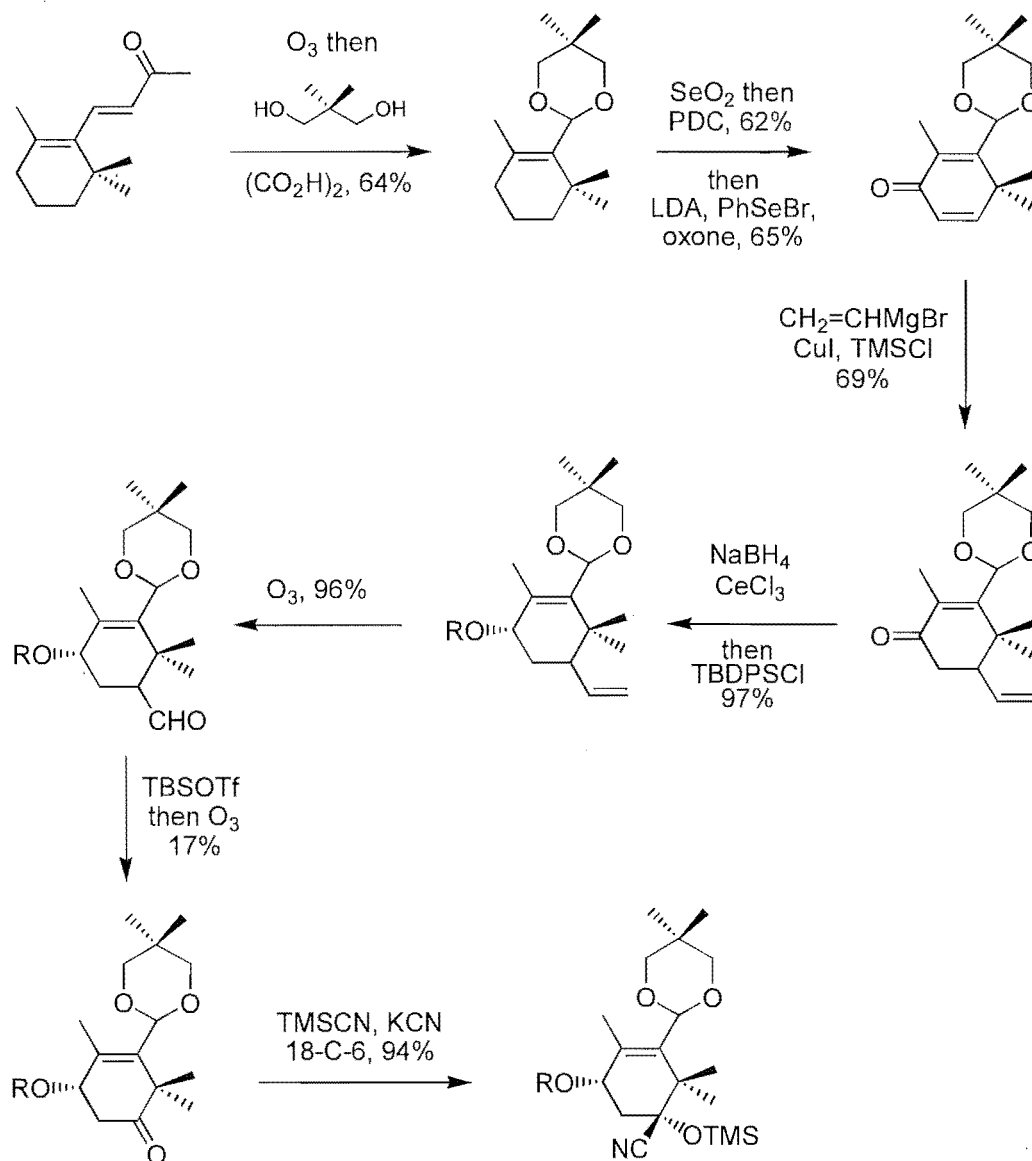


Figure 2.7 Fallis' approach to taxane A-rings beginning with β -ionone. R = *tert*-Butyldiphenylsilyl (TBDPS).

2.2 Synthesis of an A-ring from Cyclohexane-1,3-dione

A number of routes to compounds suitable for the studies in **Chapter 3** and **Chapter 4** are known.⁶¹ However, it was initially decided to develop an A-ring synthesis not based entirely on the approaches in the literature. The initial target compound was a cyclic

ketone of general type **2.1** (Figure 2.8). An overview of the retrosynthetic analysis of **2.1** is shown in Figure 2.8.

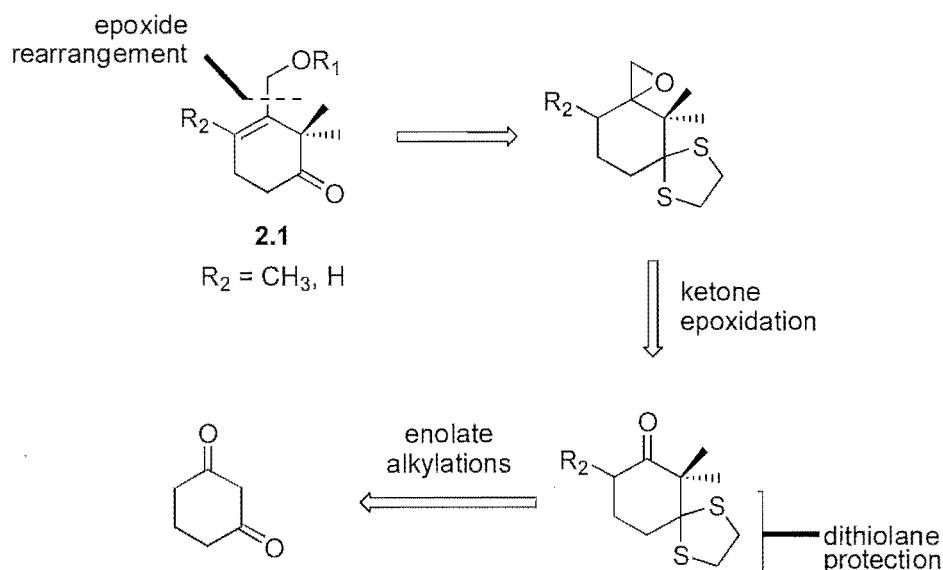


Figure 2.8 An overview of the retrosynthetic analysis of ketone **2.1**. R₁ is used to indicate a protecting group.

Cyclohexane-1,3-dione was chosen as a starting material because: (i) it is commercially available, and (ii) it contains an intact cyclohexane ring with appropriate functionality for elaboration of the *gem*-dimethyl group and the C1 and C11 (taxane numbering) functionality. Only two previous literature reports describe syntheses of taxane A-rings from cyclohexane-1,3-dione or derivatives. Given the limited disconnections that can be made for the A-ring, within the constraint of keeping the cyclohexyl ring intact, this is surprising.

Kishi and co-workers have described a taxane synthetic strategy that begins with a cyclohexane-1,3-dione derivative.⁶⁶ In the reported sequence 2,2-dimethylcyclohexane-1,3-dione was converted in four steps and 13% yield to vinyl iodide **2.2** (Figure 2.9). This work has been discussed further in Section 1.4.3.1.

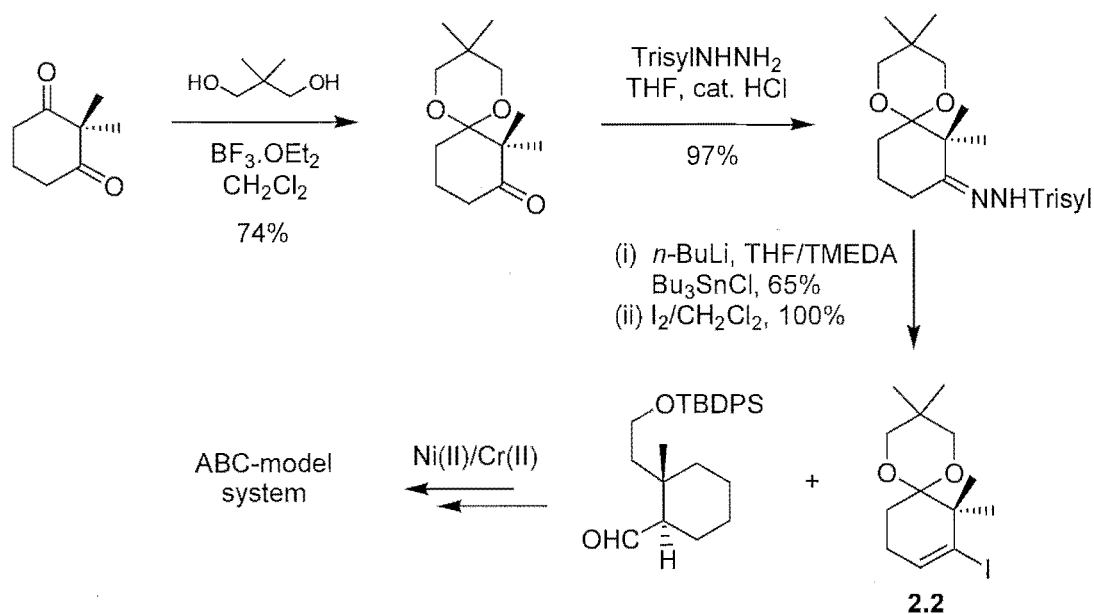


Figure 2.9 The Kishi synthesis of a taxane A-ring from 2,2-dimethylcyclohexane-1,3-dione.

The second report, by Wang and co-workers at Merck, described similar chemistry as part of a concise synthesis of a tricyclic taxane system.⁶⁷ The known cyclohexane-1,3-dione-derived monoacetal **2.3** was converted to vinyl aldehyde **2.4**, and this aldehyde was then elaborated into a tricyclic structure with the taxane skeleton (**Figure 2.10**).

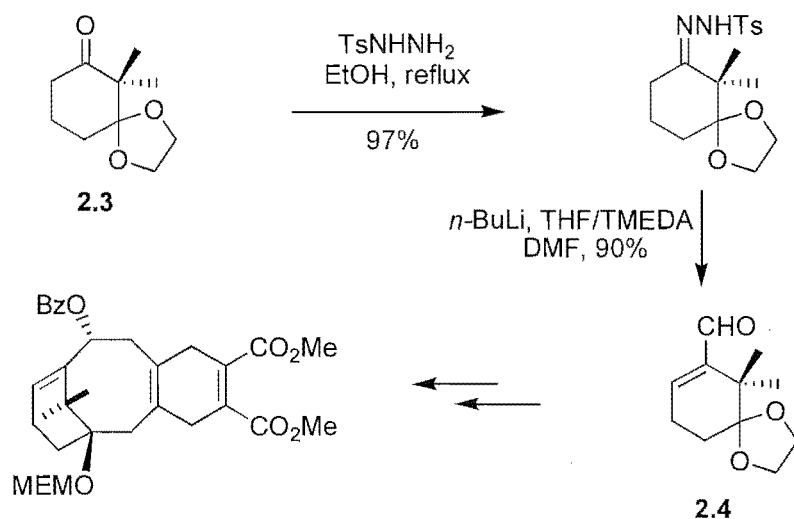
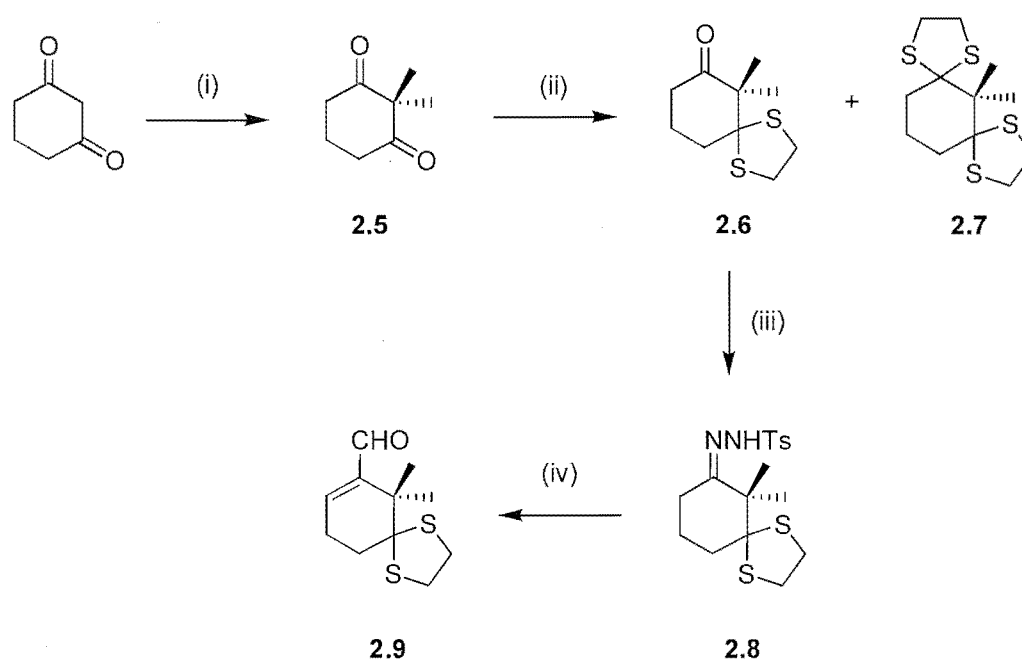


Figure 2.10 The Wang synthesis of tricyclic taxane structures from a cyclohexane-1,3-dione-derived acetal.

Based on this literature precedent, the initial steps of the synthesis developed in this thesis are shown in **Scheme 2.1**. Alkylation of commercially available cyclohexane-1,3-dione with two equivalents of methyl iodide was achieved in 57% yield by the procedure of Jacobsen and co-workers.⁶⁸ The resulting diketone **2.5** was readily monoprotected with ethane-1,2-dithiol in the presence of boron trifluoride diethyl etherate, to give ketone **2.6** in 64% yield after purification by flash chromatography.



Scheme 2.1^a The synthesis of aldehyde **2.9** by Shapiro-type reaction.

^a Reagents: (i) MeI, K₂CO₃, acetone, reflux 13 h, 57%; (ii) BF₃·OEt₂, CH₂Cl₂, ethane-1,2-dithiol, 0 °C to 25 °C, 18 h, **2.6** (64%) and **2.7** (14%); (iii) TsNHNH₂, EtOH, reflux, 2 h, 92%; (iv) *n*-BuLi (4.5 equiv.), TMEDA, -78 °C to 25 °C, 5 min, then DMF, 25 °C, 5 min, *ca* 65%.

The bis-dithiolane **2.7** was also isolated in 14% yield. Interestingly, this compound displayed unusually broad ¹³C resonances for two of the carbons (**Figure 2.11**). This feature is probably a reflection of fluxional processes that occur due to the congested environment around the *gem*-dimethyl groups and dithiolane rings.

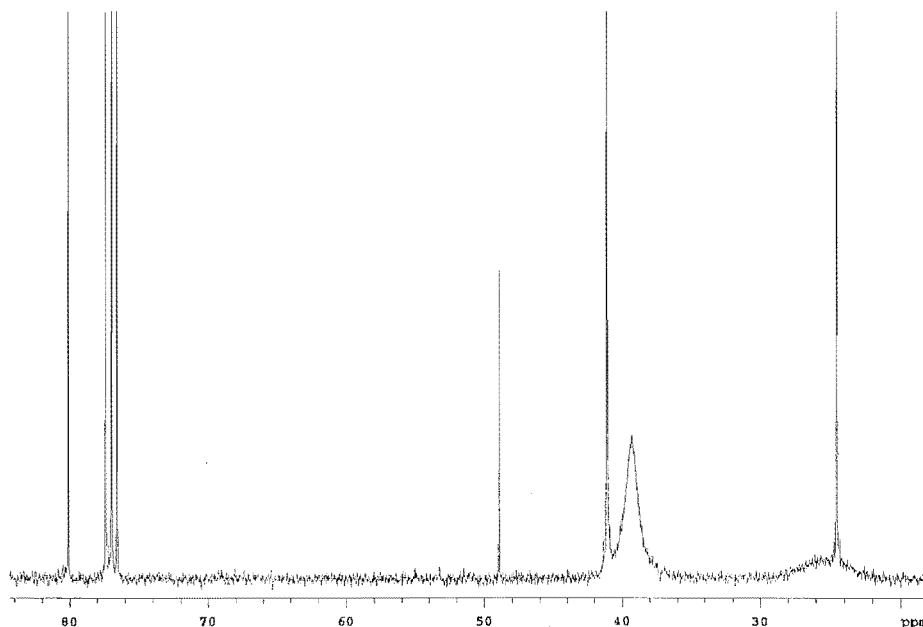


Figure 2.11 The 75 MHz ¹³C spectrum of **2.7**, which shows the unusually broad resonances that were observed.

Initially, it had been expected that elaboration of **2.6** into aldehyde **2.9** would be achievable using a Shapiro-type reaction⁶⁹ followed by 1,2-reduction using the protocol of Luche.⁷⁰ This was based on the precedent set by the groups of Kishi and Wang (*vide supra*).

However, this proved not to be the case. Preliminary investigations demonstrated that although **2.6** could be readily converted to the intermediate hydrazone **2.8**, the Shapiro-type reaction was unreliable. Yields of the aldehyde **2.9** were variable (from 0 to 65%, typically 50-60%) and the product was contaminated with the corresponding cyclohexene (10-20%) that is formed by protonation of the intermediate vinyl anion. It is possible that the problems encountered with this approach were due to lithiation adjacent to the sulfur atoms of the dithiolanes.

A potential solution to the problems encountered with the Shapiro-type approach was available *via* an epoxide isomerization first reported by Noyori and co-workers (**Figure 2.12**).⁷¹

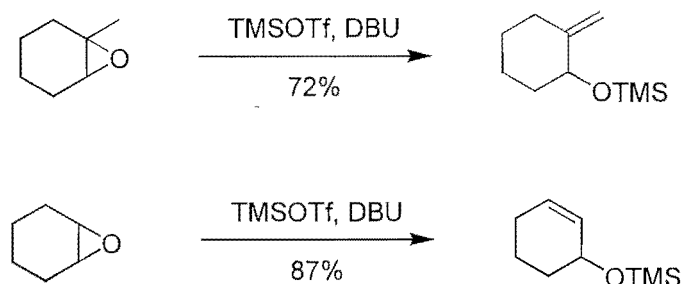
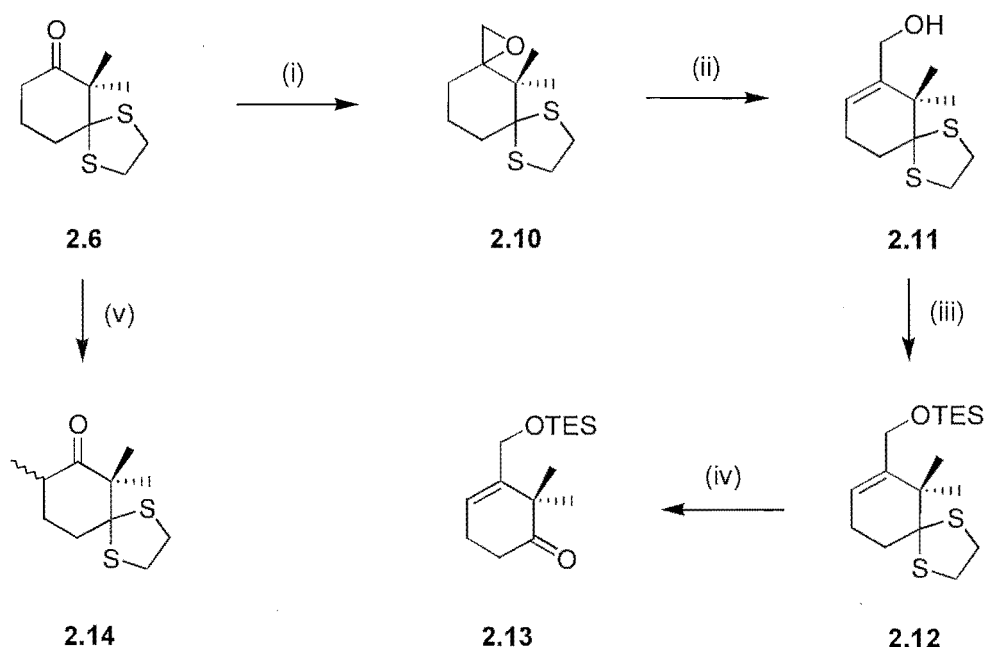


Figure 2.12 Noyori's isomerization of epoxides to allylic alcohols.

Initial efforts to epoxidize ketone **2.6** with dimethylsulfonium methylide at 0 °C were unsuccessful. This result was attributed to the sterically demanding *gem*-dimethyl group hindering reaction at this temperature. However, as shown in **Scheme 2.2** (see next page), treatment of the ketone **2.6** with excess dimethylsulfoxonium methylide at 40 °C gave the epoxide **2.10**. This compound was isolated in 95% yield after simple aqueous workup and was sufficiently pure that no chromatography was necessary.

Treatment of epoxide **2.10** with trimethylsilyl triflate and 2,6-lutidine in toluene at -78 °C for 10 minutes followed by warming to 25 °C gave, after acidic workup, the desired allylic alcohol **2.11**. This compound was obtained in 83% yield (based on returned starting material) after flash chromatography. It is important to note that on a larger scale (13 mmol), the yield of this reaction dropped to 49% (no effort was made to optimize the reaction conditions).



Scheme 2.2^a The synthesis of ketone **2.13** by epoxide isomerization.

^a Reagents: (i) NaH, Me₃S⁺(=O)I⁻, DMSO, 25 °C, 2 h, then **2.6**, 40 °C, 6 h, 95%; (ii) TMSOTf, 2,6-lutidine, PhMe, -78 °C, 10 min, then warm to 25 °C, 5% HCl quench, 83% (based on returned starting material); (iii) TESOTf, Et₃N, CH₂Cl₂, -78 °C, 1 h; (iv) AgNO₃, *N*-chlorosuccinimide, 2,6-lutidine, 80% aqueous MeCN, 5 min, 58% (for two steps); (v) LDA, THF, -78 °C, MeI, -78 °C to 25 °C, 2.5 h, 65%.

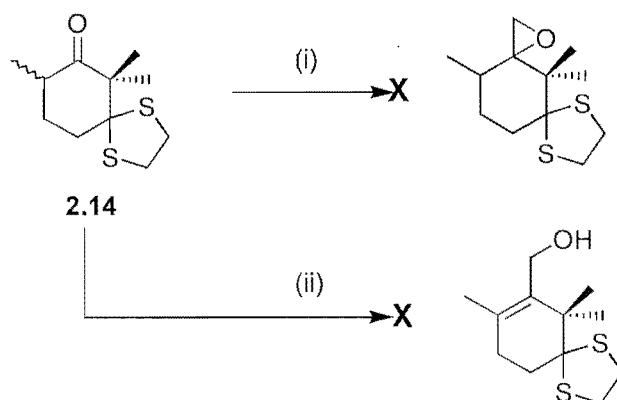
Allyl alcohol **2.11** was then protected with triethylsilyl triflate and 2,6-lutidine to give silyl ether **2.12**. It was not possible to obtain the silyl ether in analytically pure form by flash chromatography (it contained *ca* 10% of unidentified silyl impurities that co-eluted with **2.12**). Consequently, **2.12** was used in the next reaction without further purification.

An initial attempt to remove the dithiolane protecting group from **2.12** under the oxidative conditions described by Corey (*N*-chlorosuccinimide/AgNO₃) was unsuccessful. These conditions resulted in partial desilylation. However, the same procedure in the presence of 2,6-lutidine⁷² as an acid scavenger was successful.

Purification of the reaction mixture by flash chromatography gave ketone **2.13** in 58% yield (for two steps).

With a route to constructs of the desired type secured, it was possible to examine the installation of the C12 methyl group. Alkylation of ketone **2.6** was achieved under standard conditions by treatment of the ketone with lithium diisopropylamide, followed by methyl iodide to give ketone **2.14** in 65% yield [Scheme 2.2, step (v)].

Efforts to epoxidize **2.14** under the previously developed conditions (dimethylsulfoxonium methylide at 40 °C) were unsuccessful, and starting material was recovered from these reactions (Scheme 2.3). Based on the assumption that the keto group of **2.14** would be very hindered (*cf* the earlier observations regarding the reactivity of **2.6** with dimethylsulfonium methylide) a method that utilized a more reactive nucleophile was sought.



Scheme 2.3^a Attempts to epoxidize and isomerize ketone **2.14**.

^a Reagents: (i) $\text{Me}_3\text{S}^+(\text{=O})\text{I}^-$, NaH, DMSO, 40°C; (ii) (a) CH_2Br_2 , *n*-BuLi, THF, -78 °C to 25 °C, 12 h; (b) TMSOTf, 2,6-lutidine, PhMe, -78°C, 10 min, then warm to 25°C, 5% HCl quench.

An epoxide-forming process that utilizes bromomethyl lithium as the nucleophile has been reported by Mitchnick and Matteson.⁷³ Typically, a solution of dibromomethane

and the carbonyl compound in THF are cooled to $-78\text{ }^{\circ}\text{C}$, and *n*-butyllithium is added dropwise. This results in bromine-lithium exchange to give bromomethylolithium which adds to the carbonyl group. Warming of the reaction results in closure of the intermediate haloalkoxide to give epoxides.

Treatment of **2.14** under these conditions resulted in consumption of the starting material (as evidenced by ^1H nmr and TLC analysis). However, the ^1H nmr spectrum of the reaction mixture was complex and indicated the presence of several compounds. Resonances at *ca* δ_{H} 2.50 and δ_{H} 2.95 with similar coupling patterns to those observed for **2.10** were present. These resonances indicated the possibility of an exocyclic epoxide. Because of the complexity of the reaction mixture, it was decided that rather than attempting to further purify these compounds, it would be judicious to treat the mixture with trimethylsilyl triflate and 2,6-lutidine under the same conditions as used for **2.10** (see **Scheme 2.3**). However, analysis of the ^1H nmr spectrum of the crude reaction mixture after acidic workup failed to indicate the likelihood of any of the desired product.

At this juncture it was decided that efforts would be better directed at the Diels–Alder approach described in the following section. However, it is worth noting that a potential solution to the problem of installation of the allylic alcohol would be to form the enol triflate (see **Figure 2.12**, compound **2.14** to **2.15**). This would give a platform from which Pd(0) catalyzed carbonylation (**2.15** to **2.16**) or a Pd(0) catalyzed Stille-type coupling to a one-carbon unit (**2.15** to **2.17**) should be possible.

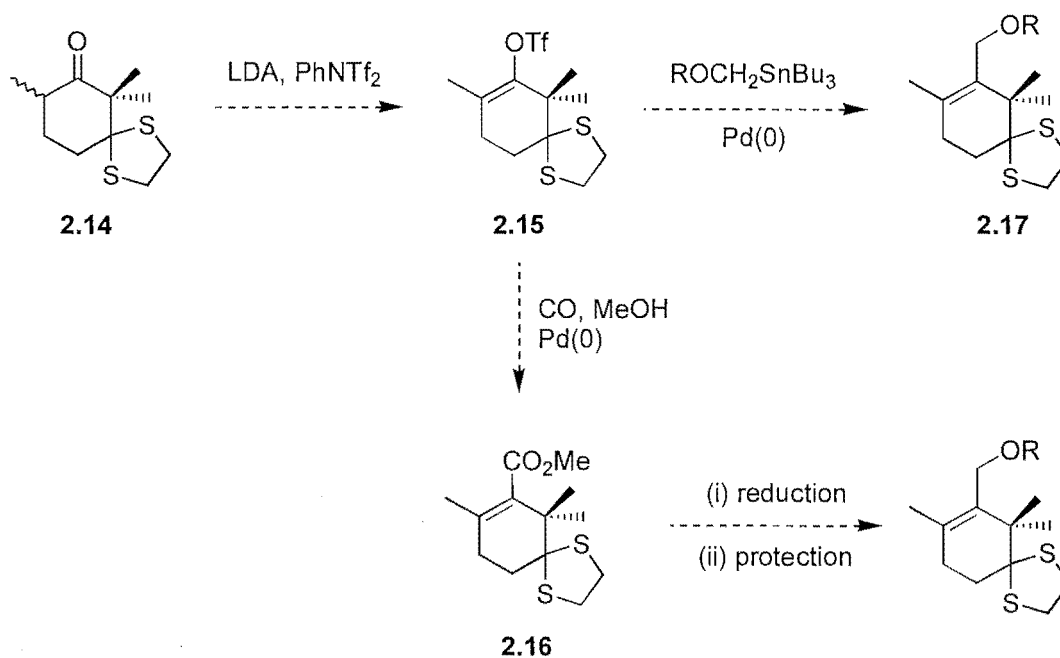


Figure 2.12 A potential method for the introduction of one-carbon units onto ketone **2.14**. R is used to indicate a generic protecting group.

After this work was completed, Toivola and Koskinen reported a sequence that was very similar to the sequence described here, and also utilized the proposed Pd(0) chemistry for the installation of the alcohol (**Figure 2.13**).⁷⁴

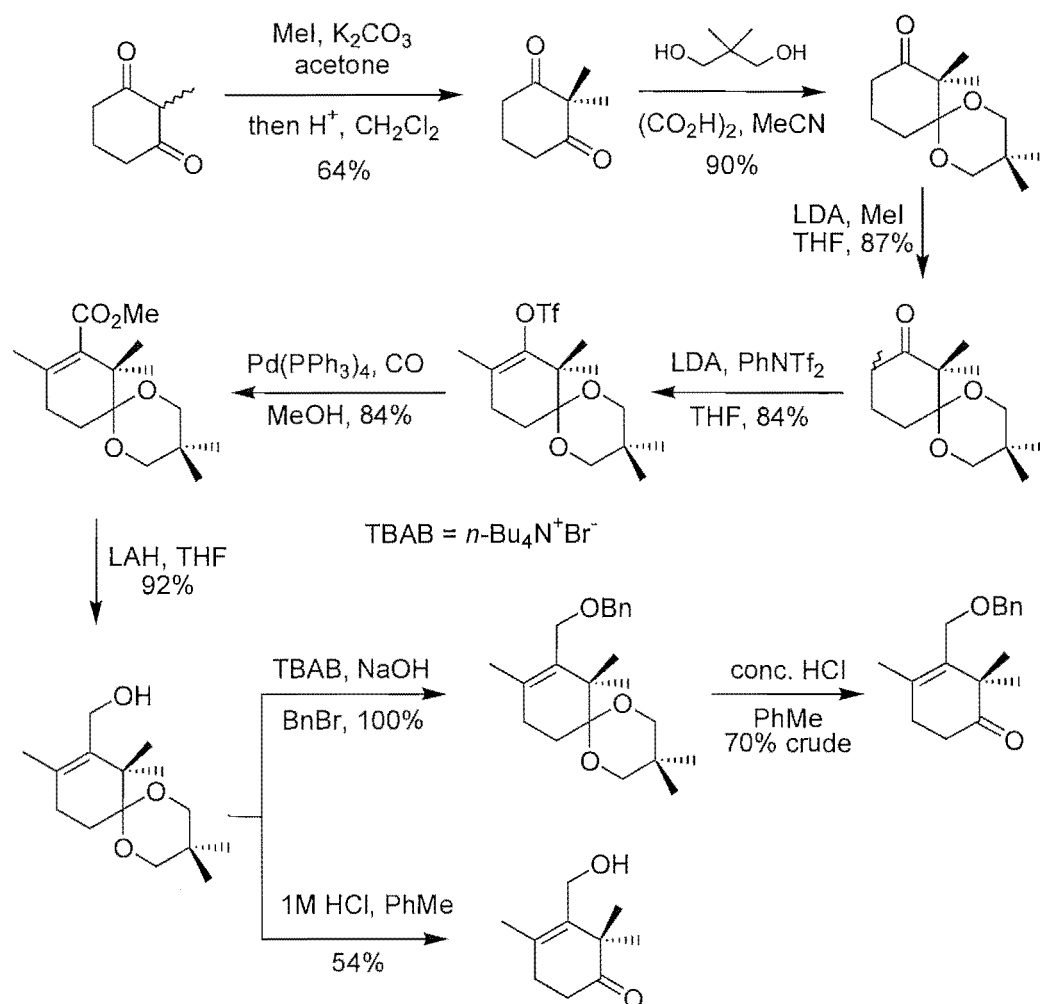


Figure 2.13 Toivola and Koskinen's synthesis of taxane A-rings.

2.3 A Diels–Alder Route to A-Ring Structures

A number of modest yielding steps, and problems with installation of the hydroxymethyl side chain in C12 methylated systems, led to the consideration of an alternative approach to the synthesis of the A-ring. The Nicolaou A-ring synthesis has demonstrated that the Diels–Alder reaction can be used to assemble A-ring structures (see **Figure 2.5**). It was expected that the reaction reported by Nicolaou and co-workers could be expanded to include a number of dienes and dienophiles that contained suitable functionality for the desired constructs (**Figure 2.14**).

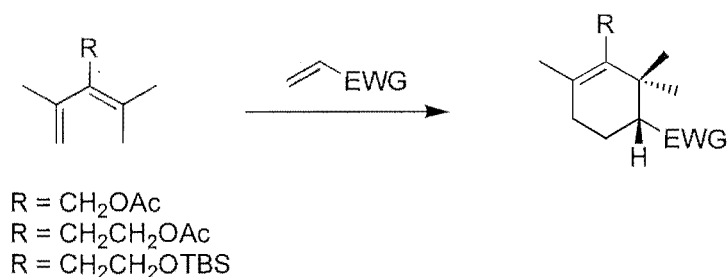


Figure 2.14 The proposed Diels–Alder synthesis of the A-ring. EWG = electron withdrawing group.

These plans were supported by the intramolecular Diels–Alder studies of Shea and co-workers, and Jenkins and co-workers.⁷⁵ Hitchcock and Pattenden have also reported an example that was directly related to the planned route (**Figure 2.15**).⁷⁶

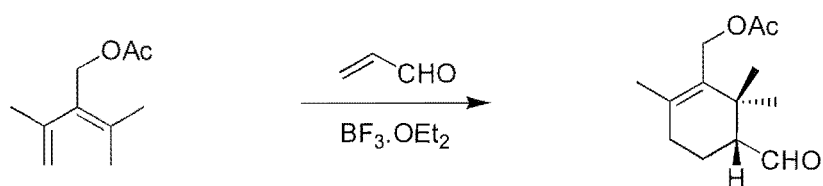
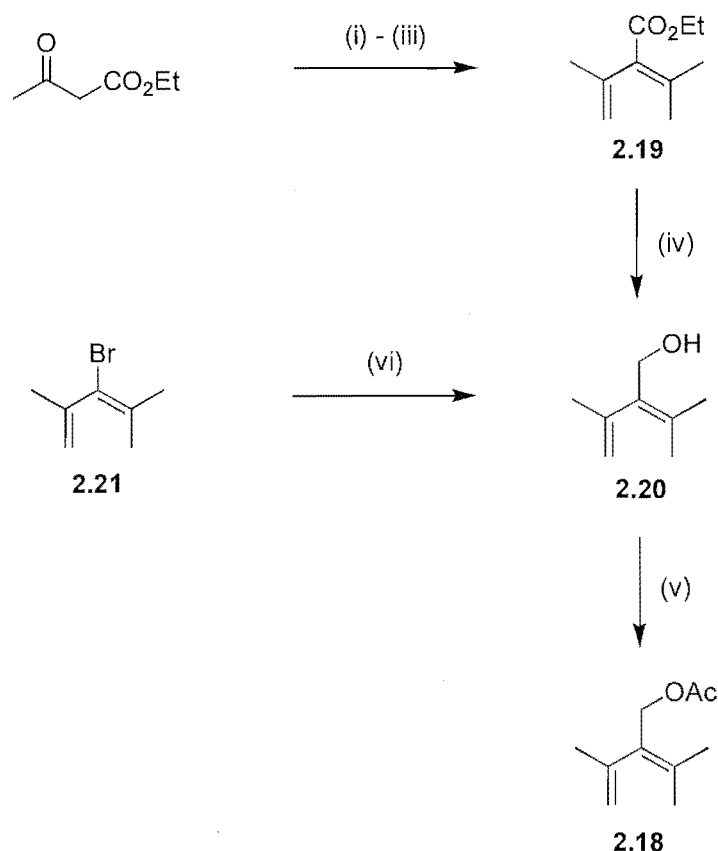


Figure 2.15 Hitchcock and Pattenden's A-ring synthesis by Diels–Alder reaction.

With good literature precedent for the proposed transformation, the initial goal was to investigate whether the reaction was possible with dienophiles other than acrolein and α -chloroacrylonitrile. These studies were conducted using diene **2.18**, the synthesis of which is shown in **Scheme 2.4**.



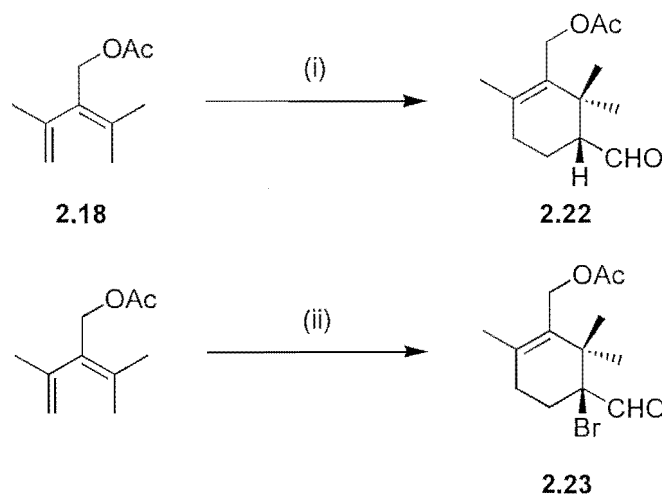
Scheme 2.4^a The synthesis of diene **2.18**.

^a Reagents: (i) acetone (2 equiv.), Ac_2O (1.2 equiv.), ZnCl_2 (0.14 equiv.), reflux, 72 h, 30%; (ii) MeMgI , Et_2O , 0 °C to 25 °C, 8 h; (iii) *p*-TsOH (0.2 equiv.), PhH, 65 °C, 3 h, *ca* 65% (over two steps); (iv) LiAlH_4 , -15 °C to 0 °C, 2 h, 87%; (v) Ac_2O , Et_3N , DMAP, CH_2Cl_2 , 0 °C to 25 °C, 1 h, 84%; (vi) (a) *t*-BuLi (2 equiv.), THF, -78 °C, 15 min, then DMF, -78 °C to 25 °C, 1 h. (b) NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, MeOH, 25 °C, 10 min, 58% (over two steps).

The first route to **2.18** utilized essentially the sequence reported by Nicolaou and co-workers in their total synthesis of paclitaxel (lithium aluminium hydride was used in the synthesis described here, whereas Nicolaou's group used diisobutylaluminium hydride). This involved the condensation of ethylacetoacetate with acetone followed by Grignard addition to the keto group and dehydration to give diene ester **2.19** (Scheme 2.4). Reduction of the ester was then achieved using lithium aluminium hydride to give the diene alcohol **2.20** in *ca* 17% yield overall for the four reactions.

The purifications involved in the Nicolaou sequence proved tedious in the author's hands. For this reason, an alternative synthesis of alcohol **2.20** was developed. This route is also shown in Scheme 2.4. Bromodiene **2.21** (*vide infra*) was treated with *tert*-butyllithium in THF at -78°C, followed by *N,N*-dimethylformamide to introduce a formyl group. The crude intermediate aldehyde was readily reduced by sodium borohydride in the presence of cerium(III) chloride using the conditions originally described by Luche and co-workers.⁷⁰ After chromatography, this sequence provided **2.20** in 58% yield (not optimized) for the two operations. Although the synthesis of **2.21** requires two steps, overall this route compares favorably with the Nicolaou route as it is higher yielding (*ca* 36% overall) and proceeds with less purification.

After acetylation of alcohol **2.20** to give acetate **2.18** under standard conditions [Scheme 2.4, step (v)], it was possible to investigate the Diels–Alder reaction. A number of initial attempts to react diene **2.18** with acrylate esters and oxazolidinone-derived dienophiles under both thermal and Lewis acid catalyzed conditions were unsuccessful. However, as previously outlined by Hitchcock and Pattenden, the reaction of the diene **2.18** with acrolein in CH₂Cl₂ using boron trifluoride diethyl etherate proceeded rapidly (within two hours at -78 °C as judged by TLC analysis). After chromatography, **2.22** was obtained in 79% yield. It also proved possible to extend this result to the use of 2-bromoacrolein as dienophile (Scheme 2.5). This reaction gave α -bromo aldehyde **2.23** in 60% yield. Although not investigated here this result may allow introduction of the C1-oxygenation by the procedure utilized by Corey¹²⁰ in prostaglandin syntheses (see Figure 2.16). It should also be noted that Yost and Funk have recently reported the direct introduction of the C1-oxygenation in taxane constructs by using 2-(acyloxy)acroleins as dienophiles.⁷⁷



Scheme 2.5^a Reactions of diene **2.18** with acrolein and 2-bromoacrolein.

^a Reagents: (i) acrolein (3.5 equiv.), $\text{BF}_3 \cdot \text{OEt}_2$ (3 equiv.), CH_2Cl_2 , -78°C , 2 h, 79%; (ii) 2-bromoacrolein (3.5 equiv.), $\text{BF}_3 \cdot \text{OEt}_2$ (3 equiv.), CH_2Cl_2 , -78°C , 2 h, 60%.

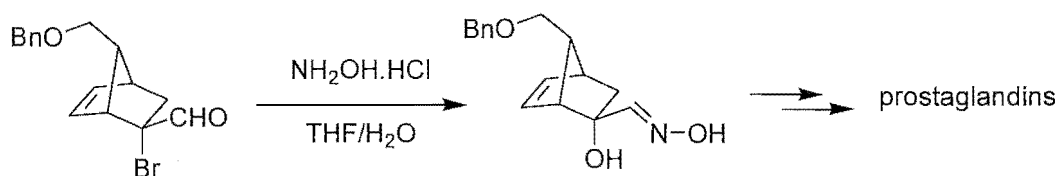


Figure 2.16 Corey's conversion of 2-bromoaldehydes to 2-hydroxy oximes as part of a prostaglandin synthesis strategy.

The regiochemistry shown for the Diels–Alder reaction is as would be expected based on frontier molecular orbital theory. Nonetheless, a full range of two-dimensional nmr experiments, including HSQC and HMBC experiments, were performed on a sample of **2.22**. The information derived from these experiments is shown in **Figure 2.17** and **Figure 2.18**. This information confirmed the connectivity to be as shown.

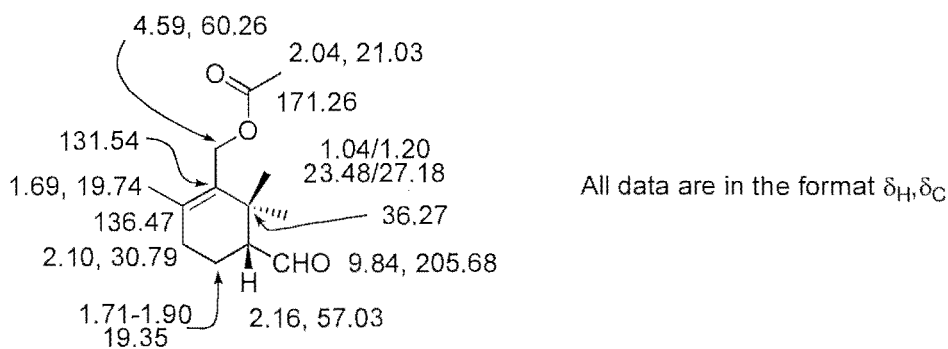


Figure 2.17 Assignment of ^1H and ^{13}C nmr data for **2.22** based on HSQC and HMBC derived information.

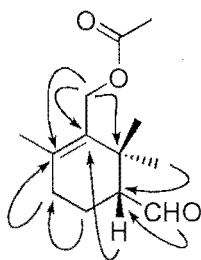
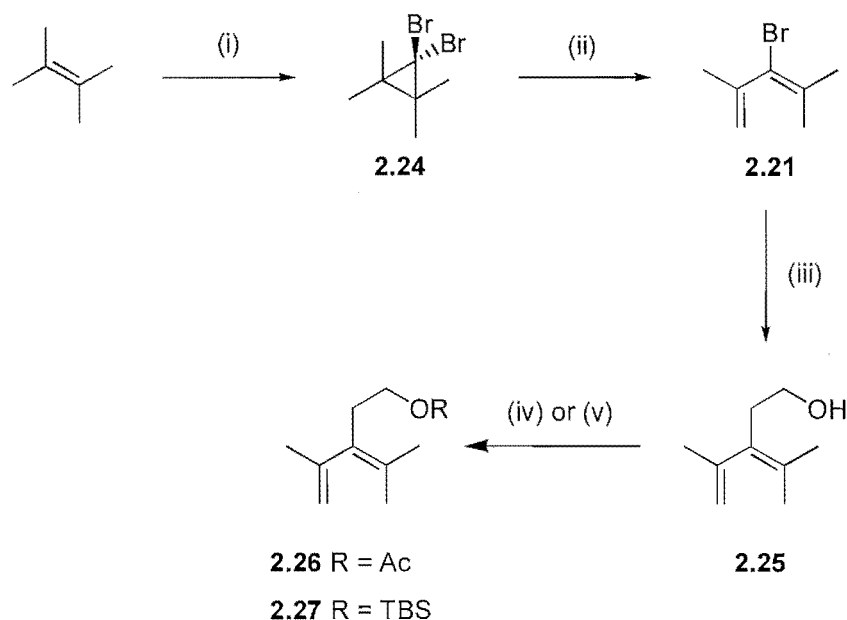


Figure 2.18 Key HMBC correlations for **2.22**.

The Diels–Alder route to A-rings established above was of significant strategic value to the ring-closing metathesis approach to an AB-ring system described in **Chapter 3**. However, it remained to be demonstrated that the chemistry could be extended to dienes containing one further carbon in the side chain. This is because the added carbon would be more useful for the direct introduction of the functionality required for the ring-closing metathesis reaction. The synthesis of the required dienes is shown in **Scheme 2.6**.



Scheme 2^a Synthesis of hydroxyethyl dienes.

^a Regents: (i) CHBr_3 , *t*-BuOK, pentane, 0 °C, 4 h, 64%; (ii) PhNMe_2 , 140 °C, 96%; (iii) *t*-BuLi, THF, -78 °C, 10 min, then ethylene oxide, -78 °C to 0 °C, quant.; (iv) Ac_2O , Et_3N , DMAP (cat.), CH_2Cl_2 , 0 °C to 25 °C, 1 h, 77%; (v) TBSCl, imidazole, DMF, 25 °C, 16 h, 82%.

Dibromocyclopropanation of 2,3-dimethylbut-2-ene with bromoform and potassium *tert*-butoxide following the procedure of Magnus and co-workers⁷⁸ gave dibromocyclopropane **2.24**.[†] It was not possible to replicate the very high yield obtained by these authors, even after a number of attempts. Nonetheless, in the author's hands this procedure gave reliable yields of *ca* 65% on a 0.1 molar scale. A significant advantage of this route is that it provides a crystalline compound of high purity. Disrotatory ring-opening of dibromocyclopropane **2.24** was achieved under the conditions reported by the same authors (heating to *ca* 140 °C with *N,N*-dimethylaniline as solvent and acid scavenger). This gave the bromodiene **2.21** in 96% yield after simple aqueous workup.

[†] The author would like to thank Professor Philip Magnus (University of Texas, Austin) for kindly providing full experimental details for this work.

Lithium-bromine exchange of the **2.21** could be effected at -78 °C in THF to give a lithiodiene. This species was readily quenched by the addition of excess ethylene oxide, and after standard aqueous workup, the desired alcohol **2.25** was obtained in quantitative yield. ¹H nmr analysis of this material showed it to be >95% pure. The alcohol **2.25** was either acetylated or silylated without any further purification to give dienes **2.26** and **2.27** in 77% and 82% yield respectively.

It is important to note that the yield of the diene alcohol dropped considerably (to 30-40%) upon efforts to scale this reaction. The problem was attributed to the difficulties in maintaining the reaction temperature at -78 °C during addition of large volumes of *tert*-butyllithium solution.[†] The stability of lithio species is known to be temperature dependent, particularly in ethereal solvents such as THF.⁷⁹ A solution to this problem was to perform the reaction in the glassware shown in **Figure 2.19**. This glassware, which is a modification of a design first described by Noyori and co-workers for prostaglandin synthesis,⁸⁰ allows for the addition of solutions *via* a spiral side arm that is immersed below the level of cooling medium. By the time the solution reaches the reaction, it has been cooled significantly. When performed in this glassware, the yield of the reaction was quantitative on a 50 mmolar scale.

Treatment of the diene **2.26** under the previously established conditions (acrolein, BF₃.OEt₂, CH₂Cl₂, -78 °C) resulted in clean transformation of the starting material into a new compound (within *one* hour by TLC analysis). Standard aqueous workup gave the Diels–Alder adduct **2.28** in quantitative yield (**Scheme 2.7**). ¹H nmr analysis indicated the product to be >95% pure.

†All temperatures reported in this thesis are *external* bath temperatures unless noted otherwise.

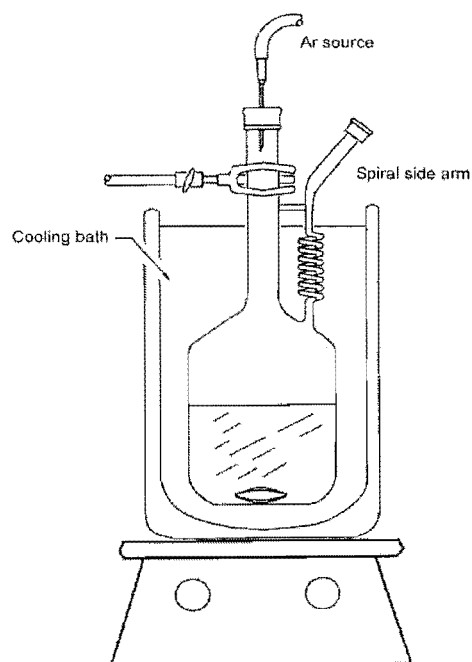
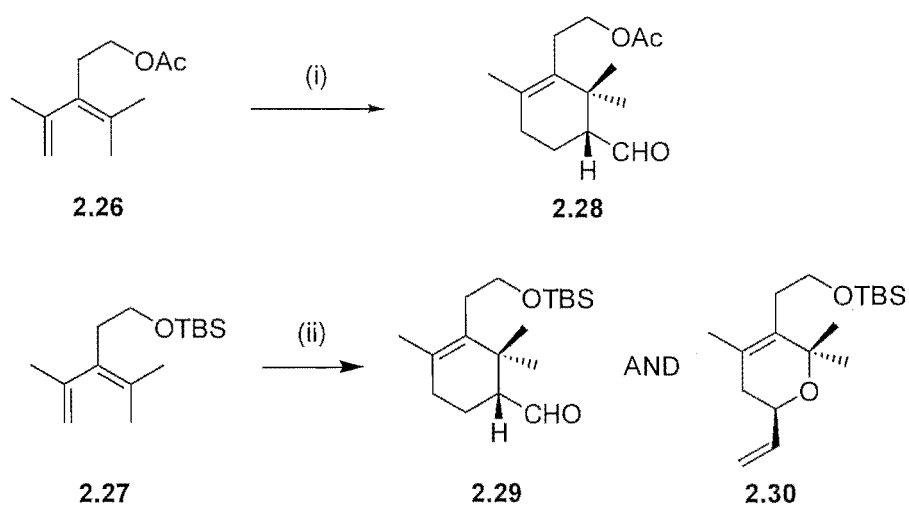


Figure 2.19 Glassware used for the large-scale synthesis of diene alcohol **2.25**.



Scheme 2.7^a Diels–Alder reaction of dienes **2.26** and **2.27** with acrolein.

^a Reagents: (i) acrolein (3.5 equiv.), $\text{BF}_3 \cdot \text{OEt}_2$ (3 equiv.), CH_2Cl_2 -78°C , 1 h, quant.; (ii) acrolein (3.5 equiv.), $\text{BF}_3 \cdot \text{OEt}_2$ (3 equiv.), CH_2Cl_2 , -78°C , 1 h, **2.29** (57%) and **2.30** (21%).

In contrast with this result, when the silyl diene **2.27** was treated under the same conditions (see also **Scheme 2.7**), analysis by TLC at one hour indicated the presence of two new compounds. After standard aqueous workup, the crude reaction mixture was analyzed by ^1H nmr, which indicated a *ca* 3:1 mixture of two compounds. The major component was the expected Diels–Alder adduct **2.29**. The minor compound gave resonances corresponding to methyl groups at δ_{H} 1.29 (integrating for 6H) and 1.68 (integrating for 3H). Other resonances observed included those belonging to a contiguous vinyl system [δ_{H} 5.12 (dt, integrating for 1H), δ_{H} 5.25 (dt, integrating for 1H), and δ_{H} 5.89 (ddd, integrating for 1H)].

It was clear from the spectroscopic data that the minor compound was closely related to the Diels–Alder adduct. Based on the data it was assigned the pyran structure **2.30** shown in **Scheme 2.7**. This compound is the hetero Diels–Alder reaction product. After purification by flash chromatography, a range of two-dimensional nmr experiments (including HSQC and HMBC) were performed. The results of these experiments, in combination with mass spectrometry, confirmed the proposed structure. The mass spectrometry fragmentation pattern for **2.30** in particular was very informative. Both the pyran **2.30** and **2.29** had retro Diels–Alder reactions as significant fragmentations from daughter ions. However, the pyran had two unique fragmentations that corresponded to the loss of H_2O and C_3H_6 . These fragmentations are possible because of the facile cleavage of the C–O bond which then allows for firstly the loss of H_2O and then C_3H_6 . This information is shown schematically in **Figure 2.20**.

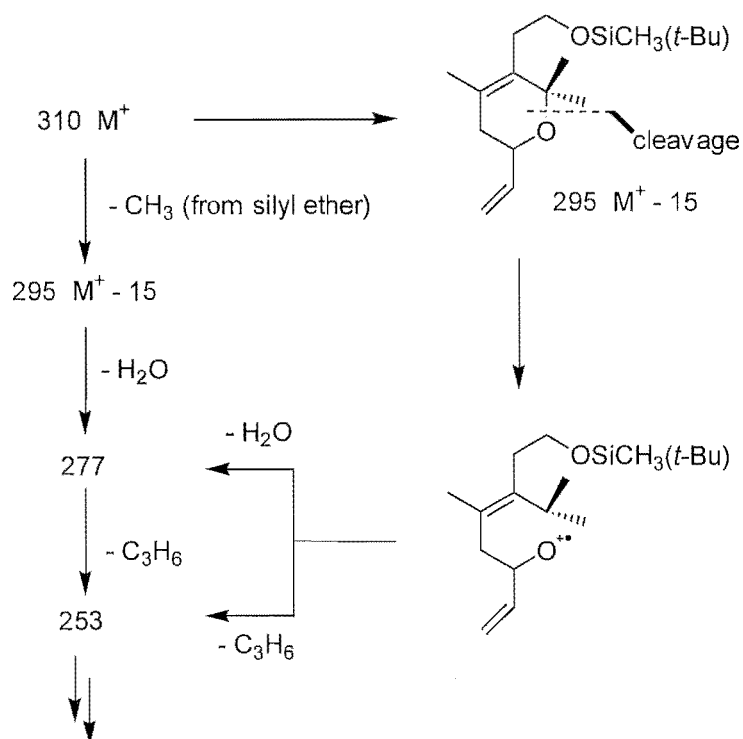


Figure 2.20 Selected mass spectrometry fragmentations for **2.29**.

The reasons for the formation of this compound under these conditions from diene **2.27** are unclear. Fallis and co-workers have recently reported similar observations for the same reaction.⁶⁵ It is also worth noting that upon careful re-examination, resonances corresponding to trace amounts (< 5%) of hetero Diels–Alder adducts were observable in spectra from earlier reactions with dienes **2.18** and **2.26**.

2.4 Summary

A linear route to a C12–desmethyl taxane A-ring has been developed. The synthesis starts with cyclohexane-1,3-dione and utilizes a trimethylsilyl triflate mediated rearrangement of an epoxide as the key step.

It was not possible to extend this chemistry to include C12–methylated substrates.

An alternative Diels–Alder approach, based on literature precedent, has also been developed. This approach has resulted in the synthesis of a number of compounds of potential use to the studies described in **Chapters 3** and **5**. This work has extended and complemented the concurrent work by Alex Fallis and co-workers (University of Ottawa, Canada).

Chapter Three

A Ring-Closing Metathesis Approach to a Taxane AB-Ring System

3.1 Introduction

Ring-closing metathesis (RCM) of acyclic dienes by complexes of transition metals such as titanium, ruthenium and molybdenum has recently come to the fore as a powerful method for carbocycle construction. Many of the advances in this area can be attributed to the development of well-defined catalyst systems. In particular, the work of Schrock⁸¹ and Grubbs,⁸² has resulted in molybdenum catalyst **3.1**, and ruthenium catalysts **3.2** and **3.3** respectively (**Figure 3.1**). These catalysts have seen widespread use in the past three years and some of their applications have been reviewed.⁸³

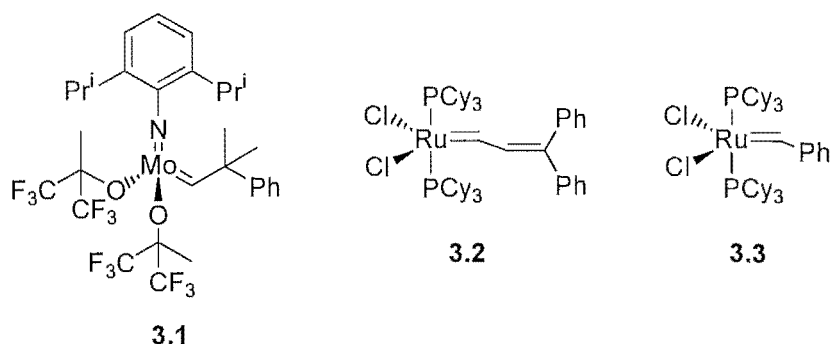


Figure 3.1 Molybdenum and ruthenium carbenes commonly used for ring-closing metathesis.[†]

[†]

Complex **3.3** is increasingly referred to in the literature as “Grubbs’ catalyst”.

A significant benefit of these catalysts is their functional group tolerance. The catalysts above, and in particular **3.3**, have been used to cyclize compounds where there are free alcohols, carbonyl groups and other potentially reactive functionality. Often functional groups such as these are incompatible with traditional methods of ring-closure, and require extensive protection.

A schematic mechanism for the RCM reaction is shown in **Figure 3.2**. Although mechanistic details for the process remain limited, a scheme of this type is adequate for understanding the process at a carbon-carbon bond forming level. Grubbs and co-workers have proposed a detailed mechanism for the ruthenium carbene mediated process and this mechanism is presented in **Section 3.2**.⁸⁴

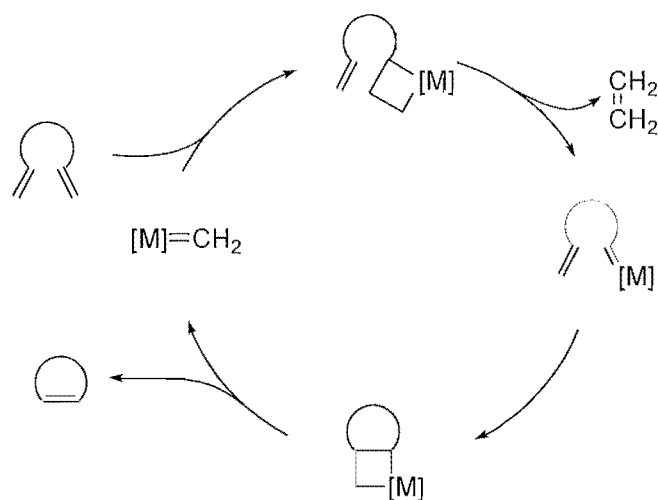


Figure 3.2 A schematic mechanism for the ring-closing metathesis reaction. [M] is used to denote the carbene and attached ligands.

A number of impressive examples of the utility of RCM to natural products synthesis already exist. For example, the broad applicability of RCM to the formation of macrolides has been demonstrated by the syntheses of fluvirucin by Hoveyda and co-

workers (**Figure 3.3**),⁸⁵ epothilone B by Danishefsky and co-workers (**Figure 3.4**),⁸⁶ and epothilone A by Nicolaou and co-workers (see also **Figure 3.4**).⁸⁷

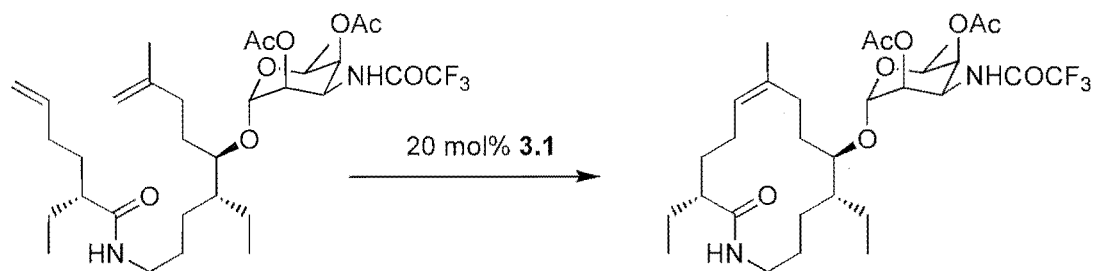


Figure 3.3 The key step of the Hoveyda synthesis of fluviricin by ring-closing metathesis.

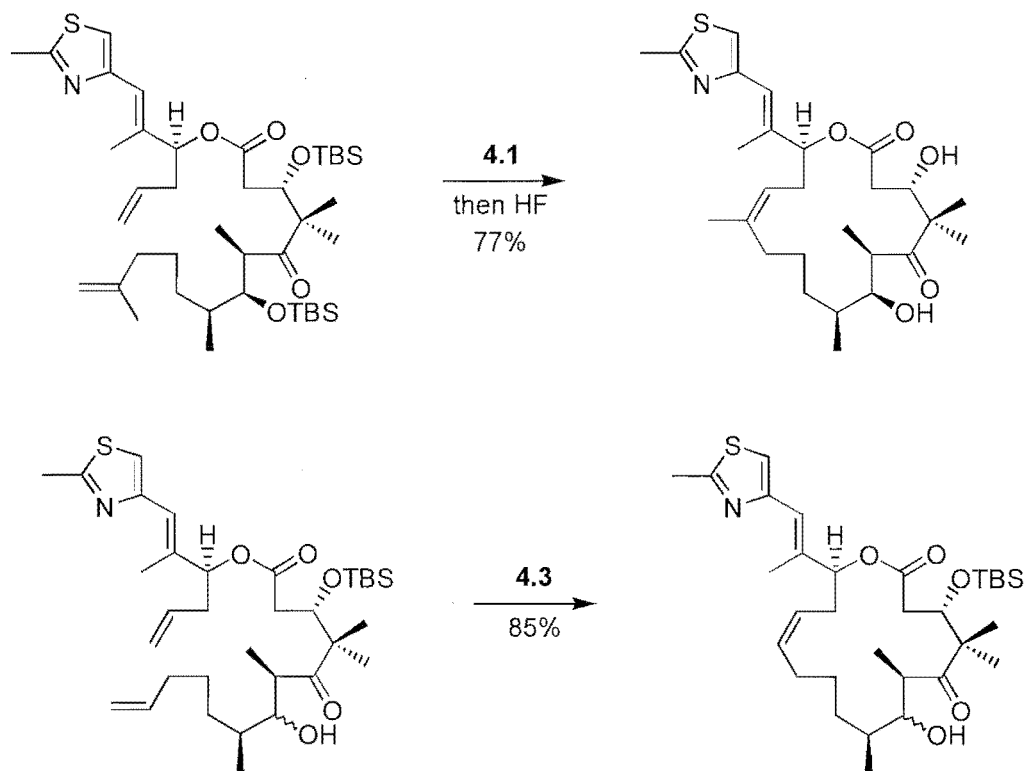


Figure 3.4 *TOP:* The Danishefsky RCM approach to epothilone B.
BOTTOM: The Nicolaou approach to epothilone A - also using ring-closing metathesis.

Along with macrocycles, many six- and seven-membered rings have been synthesized by RCM. Eight-membered rings, as is the case for so many methods, remain more difficult to access by RCM. Nonetheless, examples do exist (**Figure 3.5**).^{88,89} At such an early stage it is difficult to comment with certainty on the factors that influence the likelihood of forming an eight-membered ring by RCM. However, it would seem that the introduction of conformational constraints which predispose the compound to ring-closure can help.

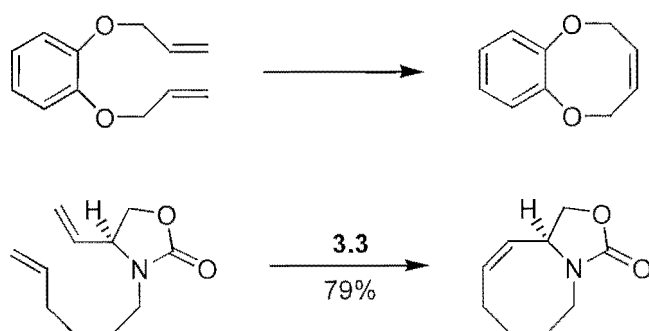


Figure 3.5 Eight-membered rings formed by ring-closing metathesis.

Fürstner and Langemann have recently presented an example that demonstrates the application of RCM to eight-membered ring synthesis as the key step of a synthesis of dactylol. This synthesis (the key step is shown in **Figure 3.6**) provided substantial reinforcement for the planned route described in this chapter.⁹⁰

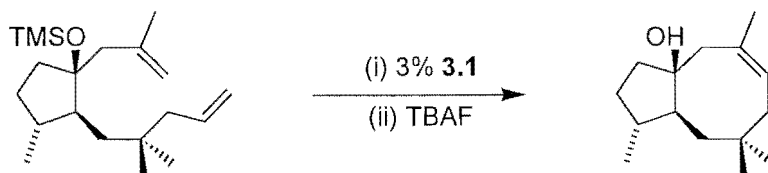


Figure 3.6 Fürstner and Langemann's synthesis of dactylol by ring-closing metathesis.

The ability of RCM to form a variety of rings attracted the author to the potential of this reaction in the setting of taxane synthesis. Ring-closing metathesis of an appropriate acyclic system (structure **3.4**, **Figure 3.7**) would result in an expedient synthesis of a taxane AB-ring system such as **3.5**. With this transformation in mind, the immediate goal was to develop a route to the necessary starting materials.

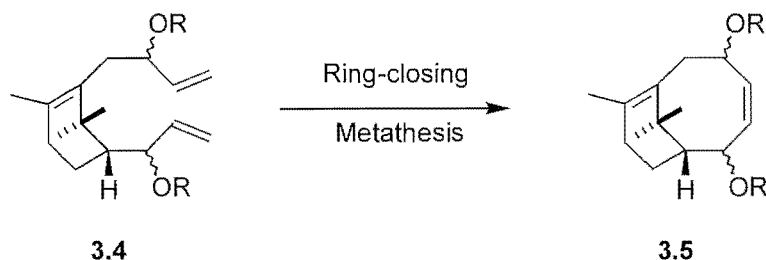
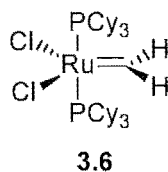


Figure 3.7 A possible RCM route to AB-ring systems. R is used to denote a generic protecting group.

3.2 The Mechanism of RCM with Ruthenium Carbenes

Although no mechanistic studies were undertaken in the work described in this thesis, it is informative to consider the currently proposed mechanism for ruthenium carbenes.⁸⁴

Grubbs and co-workers have investigated the mechanism of this reaction using carbene **3.6**.



Based on kinetic data from compound **3.6**, the general mechanism shown in **Figure 3.8** has been proposed. The experimental data was interpreted as indicating two competitive pathways. Both pathways begin by coordination of the alkene to the ruthenium. In the major pathway this is followed by phosphine loss prior to metallacyclobutane formation.

It is assumed that the required 90° rotation of the carbene relative to the alkene (or vice versa) to allow metallacyclobutane formation to occur is possible. This assumption was based on an X-ray structure that demonstrates a carbene that is rotated 45° relative to the axial ligands. Metallacyclobutane decomposition is then followed by ligand exchange to displace the metathesized alkene and regenerate a carbene. In the minor pathway, there is no loss of tricyclohexylphosphine prior to the metallacyclobutane formation.

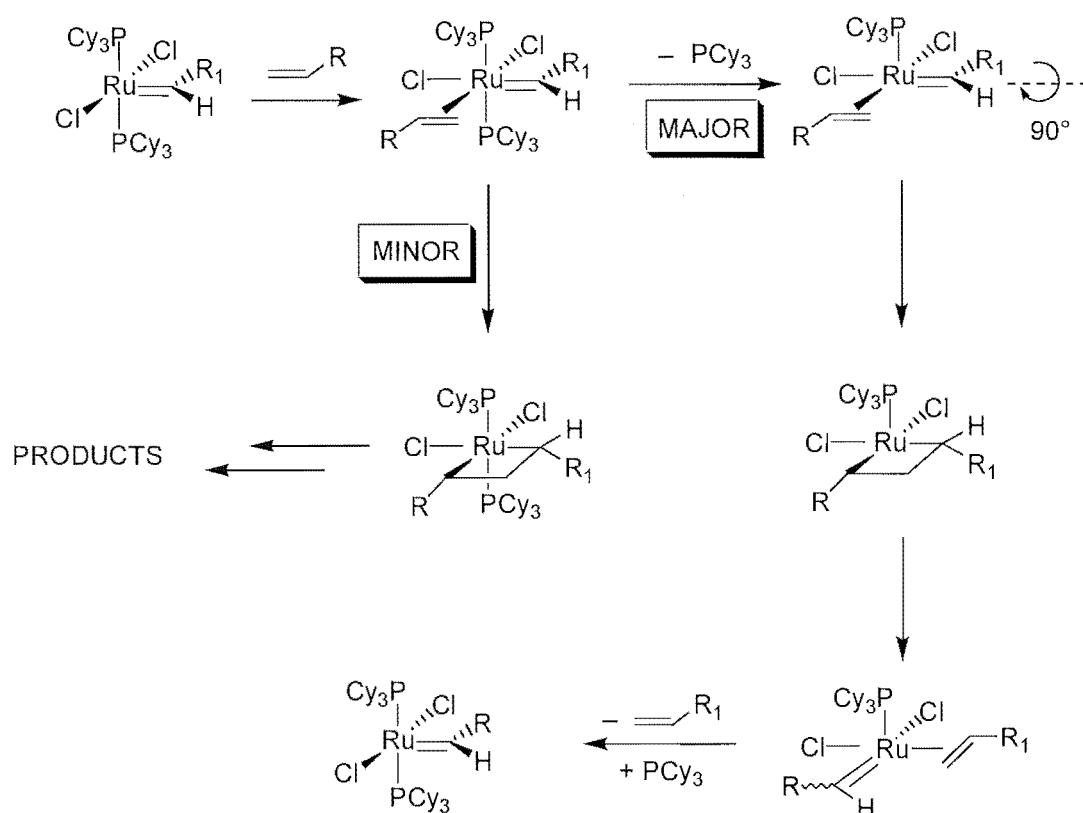


Figure 3.8 The mechanism proposed by Grubbs and co-workers for RCM with ruthenium carbenes.

Although informative, it is probably prudent to exercise caution when extending this mechanism to other carbenes. Nonetheless, it does provide a useful working model for the mechanism of the reaction.

3.3 Synthesis of the RCM Substrate

An overview of the synthetic strategy for the synthesis of the required RCM substrates is provided in **Figure 3.9**. The planned route was underpinned by the Diels–Alder chemistry developed in **Chapter 2**. It was fully expected that standard transformations of the appropriate cycloadduct would allow access to the necessary diene substrates for the RCM reaction.

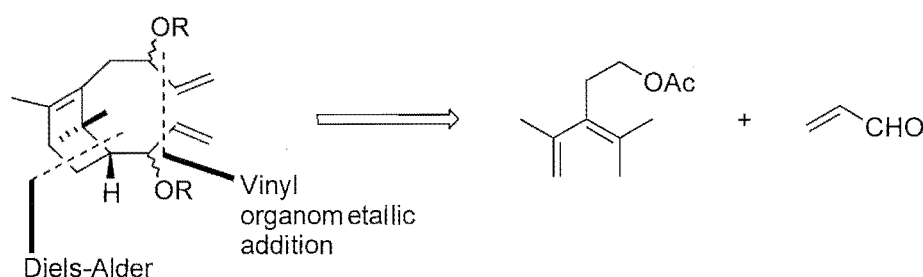
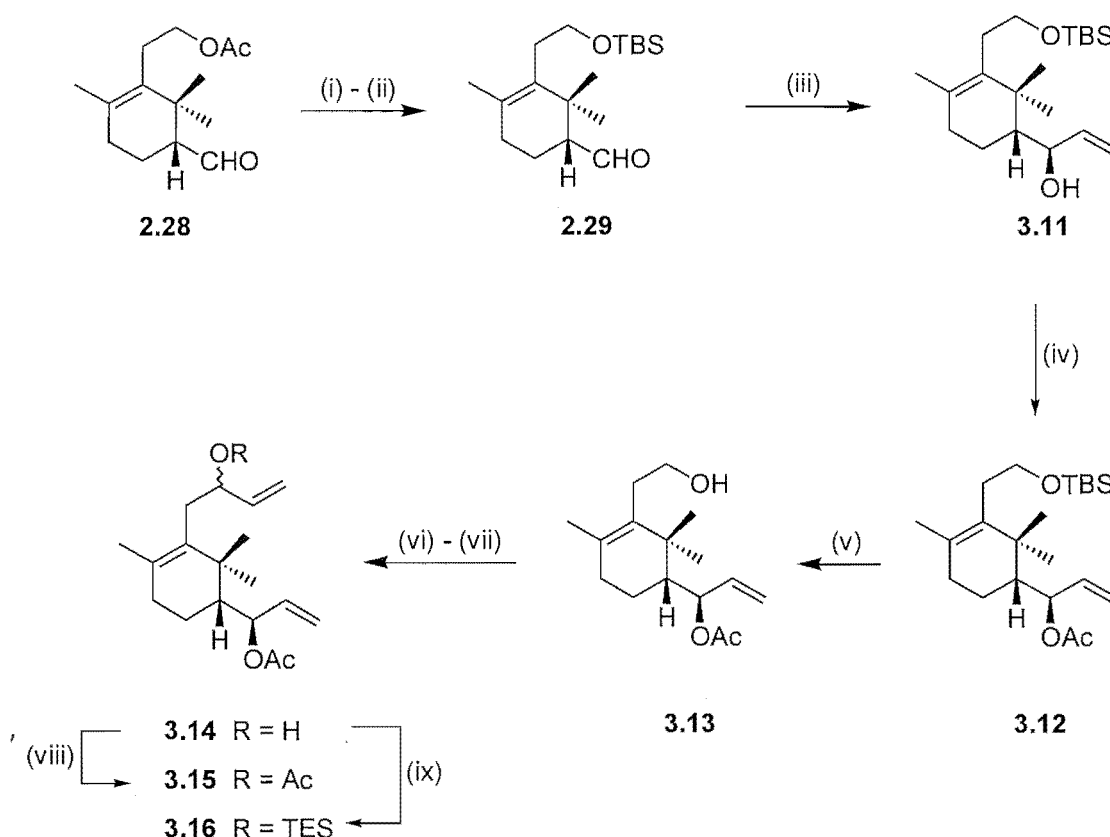


Figure 3.9 An overview of the strategy for the synthesis of substrates to test the proposed RCM closure.

With the above analysis in mind, the synthetic route developed for the synthesis of substrates to investigate the proposed RCM reaction is shown in **Scheme 3.1** (see over page).

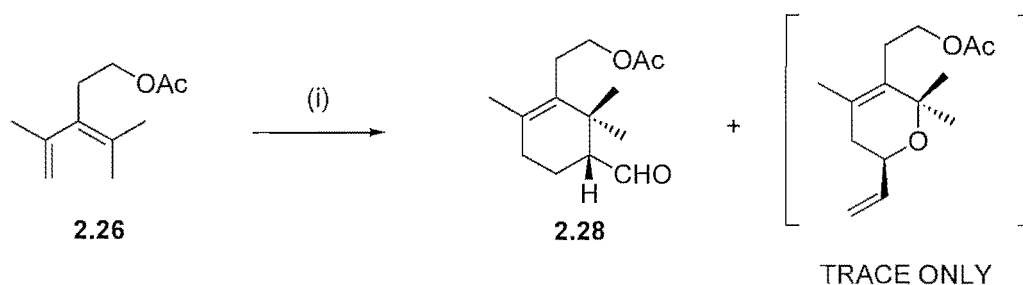


Scheme 3.1^a Synthesis of substrates to test the proposed RCM reaction.

^a Reagents: (i) K_2CO_3 (2 equiv.), MeOH- H_2O (9:1), 25 °C, 40 min.; (ii) TBSCl (1.2 equiv.), imidazole (2.5 equiv.), DMF, 25 °C, 24 h; (iii) vinylmagnesium bromide (1.2 equiv.), THF, -78 °C to -20 °C, 1 h, 53% (for 4 steps from **2.26**); (iv) Ac_2O (1.1 equiv.), DMAP (cat.), Hünig's base (1.2 equiv.), CH_2Cl_2 , 0 °C to 25 °C, 16 h; (v) TBAF, THF, 25 °C, 2 h, 74% (for two steps); (vi) DMSO, $(\text{COCl})_2$, CH_2Cl_2 , -78 °C, add **3.19**, -78 °C, 1 h, add Et_3N , -78 °C to 25 °C, 30 min; (vii) vinylmagnesium bromide (1.2 equiv.), THF, -78 °C to -20 °C, 1 h, 20% (for 2 steps); (viii) Ac_2O (1.1 equiv.), DMAP (cat.), Hünig's base (1.2 equiv.), CH_2Cl_2 , 0 °C to 25 °C, 12 h, 70%; (ix) TESOTf (1.3 equiv.), 2,6-lutidine (2 equiv.), CH_2Cl_2 -78 °C to 0 °C, 1 h, *ca* 25%.

Although the direct synthesis of **2.29** had been achieved by Diels–Alder reaction as described in **Chapter 2**, it was decided to begin the synthesis with cycloadduct **2.28**. This decision was based on the fact that the direct Diels–Alder synthesis of **2.29** was complicated by pyran formation. This necessitated chromatography to obtain **2.29** in

pure form. In contrast, the Diels-Alder reaction of **2.26** with acrolein was high-yielding and resulted in only trace levels of the corresponding pyran (**Scheme 3.2**).



Scheme 3.2^a Diels-Alder synthesis of **2.28**.

^a Reagents: (i) acrolein (3.5 equiv.), $\text{BF}_3 \cdot \text{OEt}_2$ (3 equiv.), CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 1 h, quant.

Exchange of the alcohol protecting groups was achieved by treatment of **2.28** with potassium carbonate in a 9:1 mixture of methanol-water. After standard aqueous workup, the crude material was re-protected with *tert*-butyldimethylsilyl chloride under standard conditions (DMF, imidazole, room temperature) to give **2.29** in essentially quantitative yield.

The first vinyl group was introduced by treatment of **2.29** with vinylmagnesium bromide in THF for one hour (at $-78\text{ }^\circ\text{C}$ to $-20\text{ }^\circ\text{C}$). After standard aqueous workup, the product was purified by flash chromatography to give alcohol **3.11** in 53% yield for four steps (Diels-Alder, acetate hydrolysis, silylation and Grignard addition). Analysis of the product by ^1H nmr indicated the presence of a single diastereoisomer (dr >98:2). The nmr spectroscopic data for this compound were fully assigned by two-dimensional nmr techniques and the information obtained from the HSQC and HMBC experiments is shown in **Figure 3.10**.

Although none of the intermediates in this four step sequence were purified, this was for practical reasons only. Analytical samples of all of the intermediates were obtained and

fully characterized by appropriate methods (^1H and ^{13}C nmr, IR and high-resolution mass spectrometry). These data can be found in the experimental section.

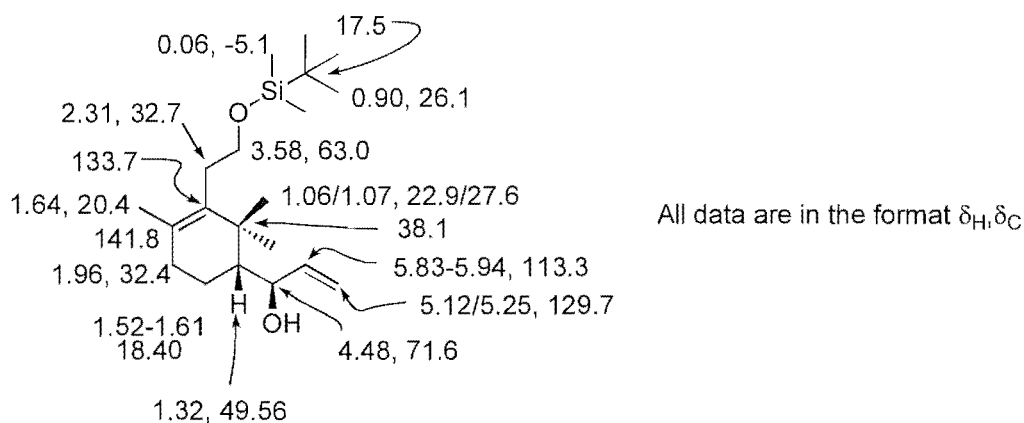


Figure 3.10 HSQC- and HMBC-based assignment of the chemical shift data for **3.11**.

Although many models have been proposed to predict or rationalize the addition of nucleophiles to carbonyl groups which have an adjacent stereogenic center, the Felkin-Anh model appears to give the most satisfactory results.⁹¹ In this model the nucleophile approaches the carbonyl group between the small and large substituents (**Figure 3.11**) on a trajectory corresponding to the Bürgi-Dunitz angle.

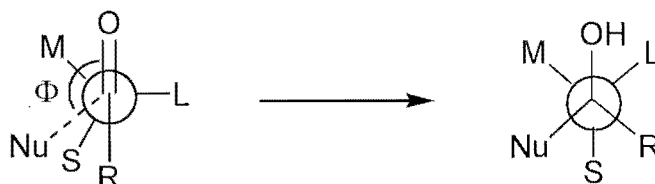


Figure 3.11 Addition of organometallic reagents to chiral carbonyl compounds with a stereogenic centre adjacent to the carbonyl group. $\Phi = 100 - 110^\circ$.

On the basis of this model, the stereochemistry of the adduct was expected to be as shown in **Figure 3.12**.[†] This corresponds to what is commonly known as the ‘Cram’ product and is in keeping with the findings of Fallis and co-workers in related studies (**Figure 3.13**).⁹² It should be noted that the stereochemistry indicated is the opposite of that found at C2 for the naturally occurring taxanes.

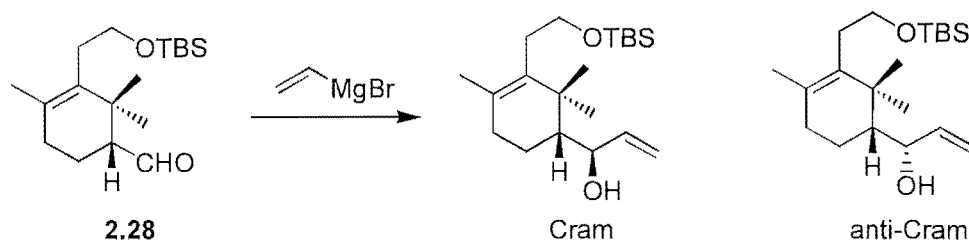


Figure 3.12 Cram and anti-Cram products from the addition of vinyl magnesium bromide to aldehyde **2.29**.

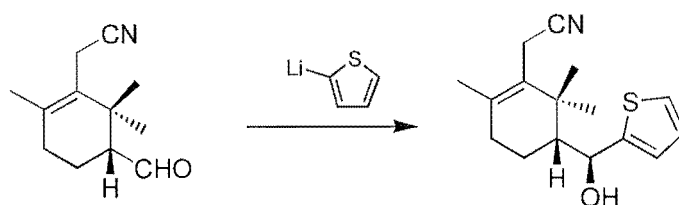
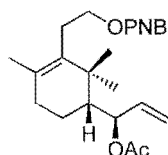


Figure 3.13 A related example from the Fallis group. The stereochemistry of the adduct was also determined from X-ray crystallography.

[†] The X-ray structure of the compound shown below has been solved and confirms the stereochemistry to be as shown:



The remarkably high diastereomeric ratio observed for this reaction was investigated further. Although isolated examples of very high diastereomeric ratios exist,⁹³ typical diastereomeric ratios for the addition of Grignard reagents to chiral aldehydes with an adjacent stereogenic center—in the absence of chelation control—range from *ca* 50:50 to 90:10 (Cram:anti-Cram).⁹⁴ It was discovered that a number of common Grignard reagents could be added to aldehyde **2.29** with high diastereomeric ratios (**Figure 3.14** and accompanying table).

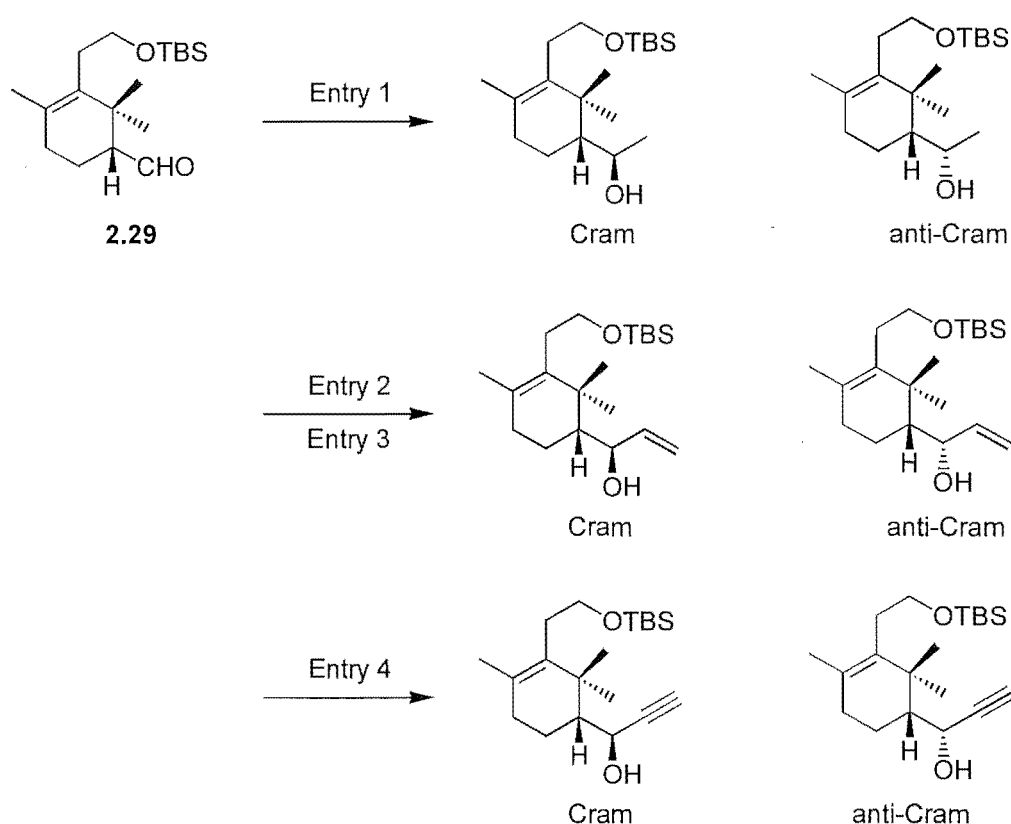
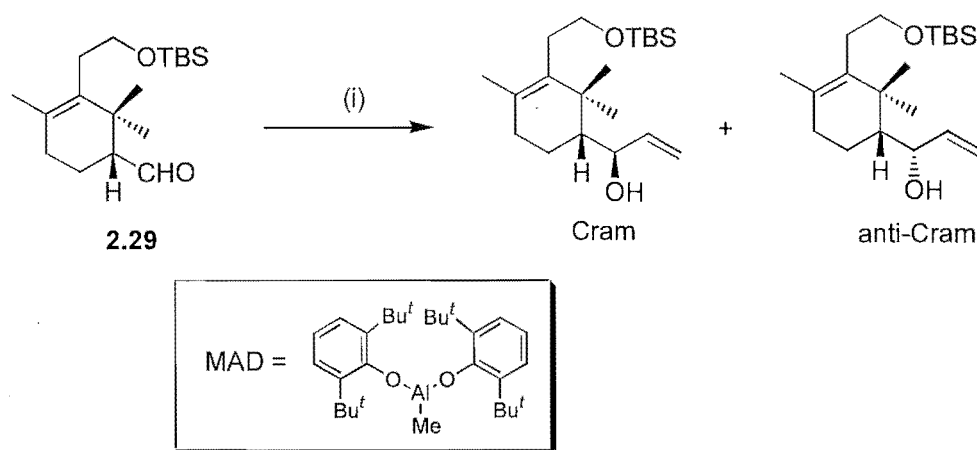


Figure 3.14 The addition of Grignard reagents to the aldehyde **2.29**. The ratio of Cram to anti-Cram adducts was determined by ¹H nmr.

A number of features are worth noting. Although there is no visible difference between sp^3 and sp^2 -hybridized reagents, small amounts (*ca* 15%) of the epimeric alcohol are observed on changing from sp^2 to sp -hybridised Grignard reagents. It is also surprising that the diastereoselection is not at all diminished by increased temperature. These observations suggest that the diastereomeric ratio is dependent on the size of the nucleophile. This assessment is in keeping with the rationale of the Felkin-Anh model.

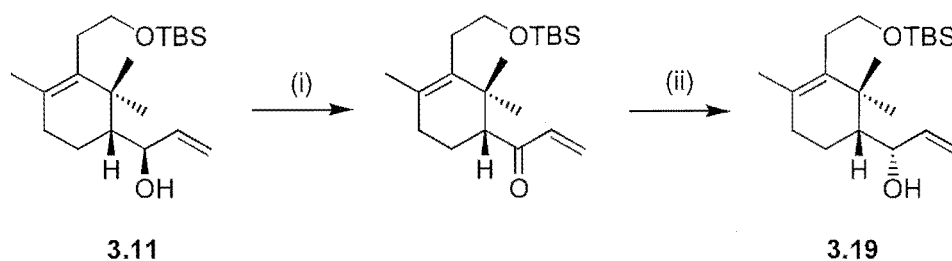
Hishashi Yamamoto and co-workers have reported the use of organometallics in the presence of bulky aluminium Lewis acids such as bis(2,6-di-*tert*-butylphenoxy) methyl aluminium (MAD) as a method of producing anti-Cram products.⁹⁵ Although the original report suggests the use of MAD or derivatives to be ineffective with sp^2 hybridized nucleophiles, this situation is likely to be substrate dependent.⁹⁶ However, the addition of vinylmagnesium bromide to aldehyde **2.29** in the presence of MAD (**Scheme 3.3**) failed to show any change in the diastereomeric ratio (>98:2 Cram:anti-Cram).



Scheme 3.4^a Attempts to alter the facial selectivity of the vinylmagnesium bromide addition to aldehyde **2.29** with MAD.

^a Reagents: (i) vinylmagnesium bromide, MAD, toluene, -78 °C, >98:2 Cram:anti-Cram.

To ascertain that the diastereomeric alcohol was not present in the reaction of **2.29** with vinylmagnesium bromide, an authentic sample was synthesized by a simple oxidation-reduction sequence (**Scheme 3.4**). All efforts to invert alcohol of **3.11** by the Mitsunobu reaction were unsuccessful.



Scheme 3.5^a Inversion of stereochemistry of the alcohol for **3.17**

^a Reagents: (i) DMSO, (COCl)₂, CH₂Cl₂, -78 °C, add **3.17**, -78 °C, 1 h, add Et₃N, -78 °C to 25 °C, 30 min; (ii) DIBAL-H (1.5 equiv.), CH₂Cl₂, -78 °C, 10 min, 48% (for two steps).

Oxidation of the allylic alcohol proceeded smoothly under the conditions originally described by Omura and Swern¹⁰⁹ to give a crude enone that was immediately dissolved in CH₂Cl₂ and cooled to -78 °C. Reduction of the keto group with diisobutylaluminum hydride (DIBAL-H) was complete within 10 minutes (by TLC analysis). The reaction was worked up and the crude product analyzed by ¹H nmr. This analysis showed *ca* 3:1:3 mixture of the diastereomeric alcohols and the product derived from 1,4 conjugate addition of the hydride. Alcohol **3.19** could be separated from these other products, and was obtained in 48% yield for the two steps.

With **3.19** in hand it was possible to re-examine the ¹H nmr spectrum for the original Grignard addition reaction (**Scheme 3.1**). Close inspection indicated that the reaction gave only a single diastereoisomer (subject to the detection limits), as none of the signals corresponding to **3.19** were visible. Selected diagnostic data for the two diastereoisomers is presented in **Figure 3.15**.

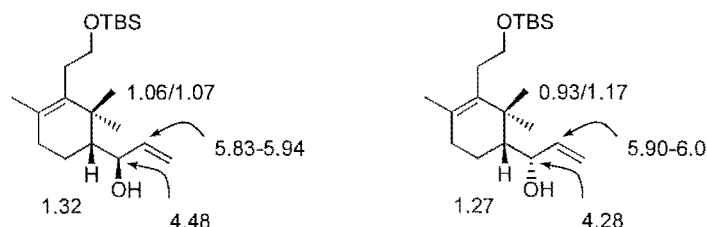


Figure 3.15 Selected diagnostic ¹H nmr data for compounds **3.11** and **3.19**.

Returning to the sequence in **Scheme 3.1**, the next step in the synthesis of the substrate for the proposed RCM reaction was protection of the allylic alcohol [**Scheme 3.1**, step (iv)]. The earlier unsuccessful efforts to invert the stereochemistry of this alcohol by Mitsunobu reaction had indicated that protecting this alcohol might be difficult. Indeed, this proved to be the case with efforts to protect the alcohol with chloromethyl methyl ether (MOM-Cl), benzyl bromide, and *tert*-butyldimethylsilyl chloride all failing to yield the desired compounds, even after prolonged reaction times. Fortunately, it did prove possible to acetylate the alcohol under standard conditions (acetic anhydride, triethylamine, and catalytic *N,N*-dimethylaminopyridine; dichloromethane as solvent; 16 hours) to give acetate **3.12**, in essentially quantitative yield. It is not clear why the alcohol failed to react with the reagents for the installation of the other protecting groups. However, it should be noted that the acetylation took a relatively long period to proceed to completion. At face value, it may be that the slow rate of reaction is due to steric effects.

The crude acetate **3.12** was smoothly desilylated with tetra-*n*-butylammonium fluoride in tetrahydrofuran at room temperature. After workup, and purification by flash chromatography, alcohol **3.13** was obtained in 74% yield (for two steps).

Oxidation of alcohol **3.13** under the conditions of Omura and Swern gave an unstable intermediate aldehyde which was immediately dissolved in tetrahydrofuran and cooled to $-78\text{ }^{\circ}\text{C}$. Treatment of this solution with vinylmagnesium bromide at $-78\text{ }^{\circ}\text{C}$ to $-20\text{ }^{\circ}\text{C}$ for one hour gave, after aqueous workup and purification by chromatography, alcohol **3.14** (as a *ca* 60:40 mixture of diastereoisomers of undetermined relative stereochemistry). The yield for these two steps was a disappointing 20%, although no effort was made to optimize either step.

This alcohol was then either acetylated (70%) under standard conditions, or silylated with triethylsilyl triflate (25%) to give RCM substrates **3.15** and **3.16** respectively. A ^1H nmr spectrum of compound **3.15** is shown in **Figure 3.16**.

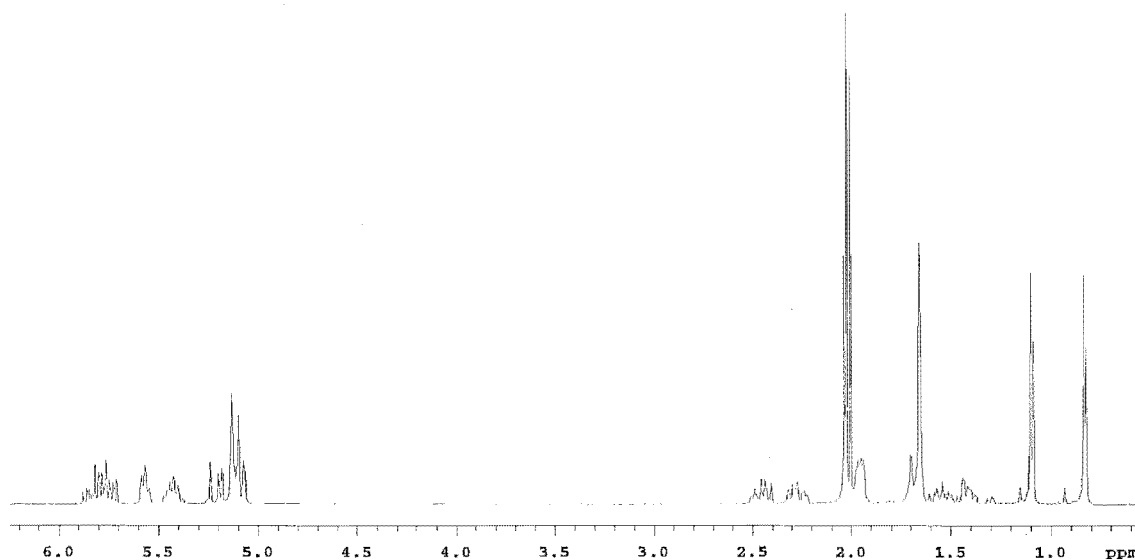
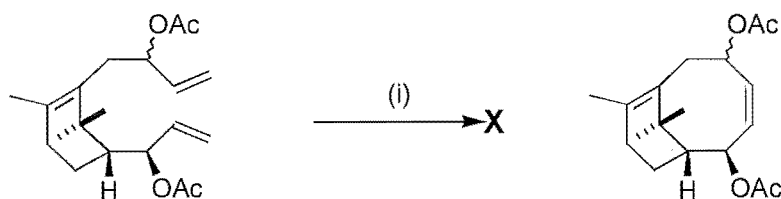


Figure 3.16 The 300 MHz ^1H nmr spectrum of the 60:40 mixture of dienes **3.15**.

With RCM substrates **3.15** and **3.16** in hand it was possible to examine the ring-closing metathesis reaction.

In the initial experiment (**Scheme 3.6**) a *ca* 60:40 mixture of dienes **3.15** was dissolved in *freshly distilled* CH_2Cl_2 that had been degassed by three freeze–pump–thaw cycles.[†] Grubbs' catalyst (**3.3**, 10 mol%), dissolved in a small volume of degassed CH_2Cl_2 was added *via* syringe. The reaction was then heated to reflux under an argon atmosphere.



Scheme 3.6^a The initial attempted RCM closure.

^a Reagents: **3.3** (10 mol%), CH_2Cl_2 , reflux, 16 h.

Analysis of the reaction by both TLC and ^1H nmr (by removing 50 μL aliquots, evaporation and dissolution in CDCl_3) at elapsed times of one hour, two hours, four hours and 16 hours indicated that the starting materials were still present. At this point the reaction was stopped by evaporation of the solvent. Disappointingly, analysis of the residue by ^1H nmr failed to show any indication of the desired products.

It was considered that two factors might be affecting the [lack of] reaction. The first was temperature, and the second was the possibility of the formation of stable coordinated carbenes. Fürstner and Langemann have investigated the possibility that this second factor may be a general problem with RCM reactions (see **Figure 3.17**).⁹⁷ Their results demonstrated that the use of tetra(isopropoxy)titanium(IV) as an additive can be beneficial.

[†] Although the literature suggests that ruthenium carbene **3.3** can be used without substantial need for inert atmosphere or dry, oxygen-free solvents, in the author's experience, these precautions are beneficial.

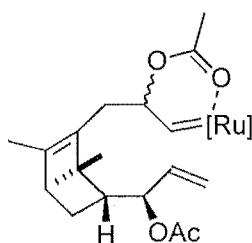


Figure 3.17 A possible stable coordinated carbene for the RCM substrate **3.15**.

Based on the possibility that the temperature might not be sufficiently high to allow cyclization, the conditions were changed to use benzene at reflux. However, these conditions also failed to give any of the desired compound. Similarly, the addition of tetra(isopropoxy)titanium(IV) to another reaction in benzene at reflux also failed to yield the desired compound.

The rate of RCM by carbene **3.1** is known to be faster than the ruthenium catalysts and it is also known to be less sensitive to steric effects.⁹⁸ However, treatment of diene **3.15** with this complex in benzene (10 mol% **3.1**, reflux, 6 h) again failed to yield any cyclized compound.

The reaction of TES-protected diene **3.16** in benzene was also examined (10 mol% **3.3**, PhH, reflux, 16 hours) but this too failed to result in cyclization.

At this juncture, it was concluded that the proposed RCM closures for **3.15** and **3.16** were not possible. The reasons for the failure of this method of ring-closure remain unclear. However, it is possible that the stereochemistry of the C2 substituent is important. Cyclization of these systems would result in a system in which there is a potential transannular interaction between this substituent and one of the methyl groups of the *gem*-dimethyl system (see **Figure 3.18**). This interaction may be reflected in an

increased activation energy for the reaction, thus rendering the process unfavorable under the conditions examined. It should be noted that the inversion of the stereochemistry at the C2 position has been achieved (**Scheme 3.5**) so it would be possible to test this hypothesis. However, the lack of further material precluded further investigation, and it was thought that efforts at this stage of proceedings would be better directed elsewhere.

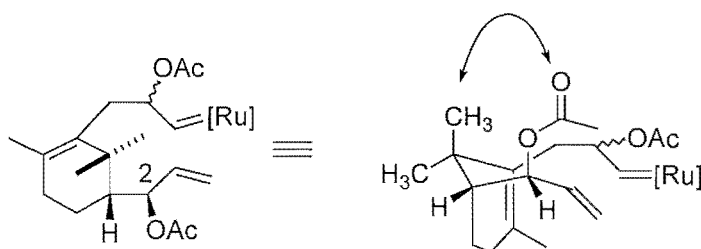


Figure 3.18 Potential transannular interactions in the metathesis reaction of diene **3.15**.

3.4 Summary

A concise synthesis of diene precursors suitable for exploring the possibility of RCM as a method for the closure of a taxane AB-ring system has been developed.

This synthesis involves a highly diastereoselective Cram-type addition of vinylmagnesium bromide to aldehyde **2.29** (dr >98:2 Cram:anti-Cram). This reaction was investigated further and it was shown that several other Grignard reagents could also be added to **2.29** with high levels of diastereoselection.

The ring-closing metathesis reaction was unsuccessful under a number of conditions examined. Although the reasons for the failure are unclear it is possible that stereochemical issues may be of significance.

Chapter Four

Ring-Closing Metathesis for the Introduction of the C-Ring

4.1 Introduction

It is clear from the total syntheses of taxusin and paclitaxel by Holton, Wender and Mukaiyama that the introduction of a C-ring onto either AB-ring constructs or B-ring systems is a significant challenge (see **Chapter 1** for a more detailed analysis of these syntheses). Typically the introduction of three to five carbons and associated oxygenation requires 15-20 steps. Although Nicolaou and Kuwajima chose to introduce the C-ring at an earlier stage, this resulted in syntheses that are dominated by protecting group chemistry. The Danishefsky synthesis of paclitaxel, and the syntheses of taxusin by Kuwajima and Paquette deal with many of these problems in a more concise manner.

The application of RCM to the problem of formation of the taxane C-ring would offer a number of advantages over current methods. Most notably it would allow the use of relatively inert functional groups (alkenes) as the direct precursors. Apart from the ease with which such alkenes could be introduced onto an AB-ring system (**Figure 4.1**), it is also conceivable that this functionality could be introduced early in a synthesis and the cyclization postponed until later (**Figure 4.2**).

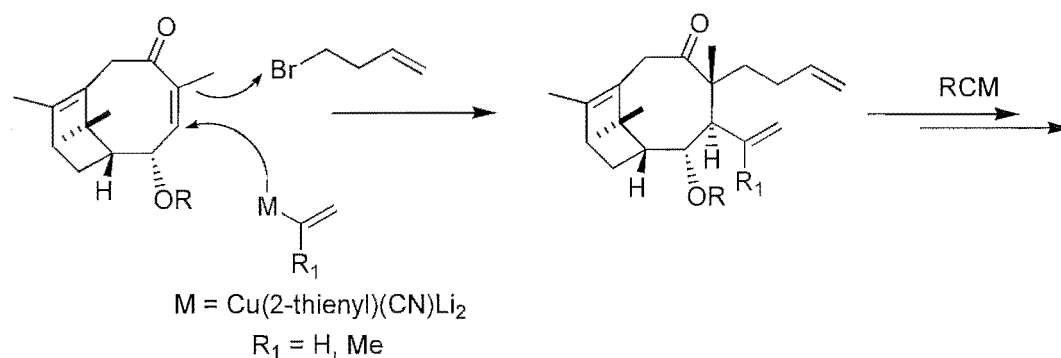


Figure 4.1 Potential for the introduction of the diene by tandem vicinal difunctionalization. R is used to denote a generic protecting group.

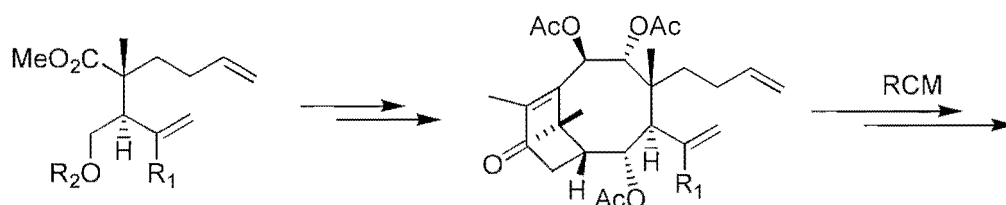


Figure 4.2 Early introduction of the diene and use as a 'protected' precursor to the C-ring. R is used to denote a generic protecting group.

It was also envisaged that the products of RCM closures should also be able to be readily converted into the typical C4/C5-oxygenation patterns found in naturally occurring taxanes (**Figure 4.3**).

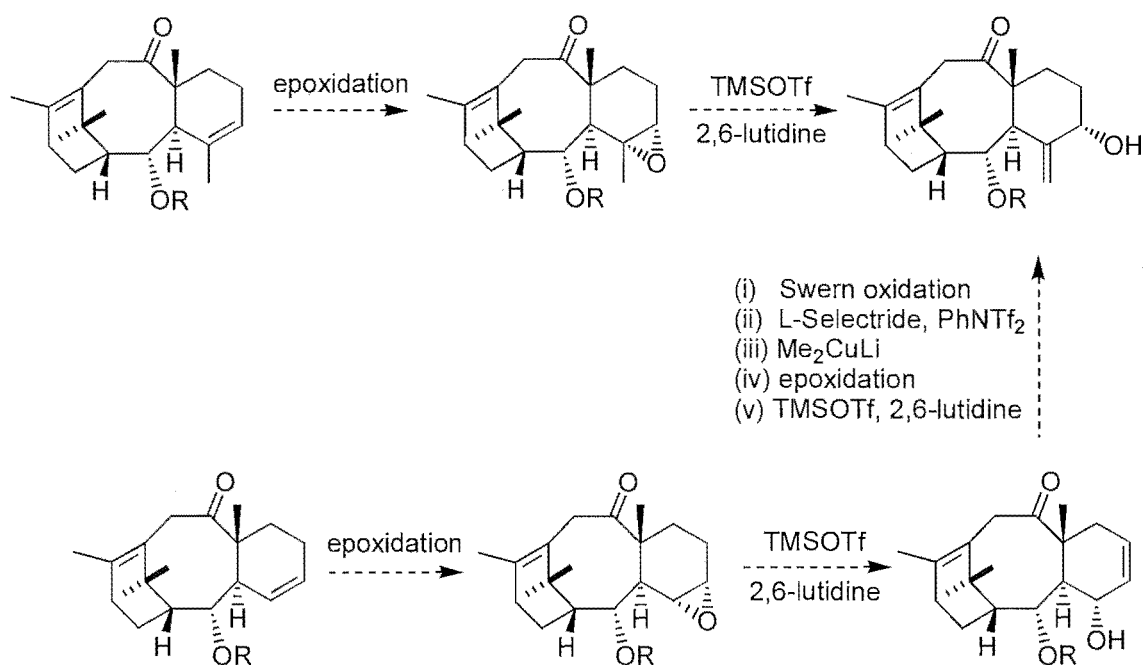


Figure 4.3 Potential introduction of oxygenation *via* epoxide isomerizations. R is used to denote a generic protecting group.

These features were all expected to provide for a versatile and concise approach to the formation of the C-ring.

The synthesis of six-membered rings by ring-closing metathesis (RCM) with the carbene complexes shown in **Figure 4.4** is well known in the literature.⁸³ However, there are few examples of its use to form fused bicyclic rings. Some examples, a number of which appeared whilst this work was in progress, or after its completion, are presented below in **Figures 4.5 – 4.8**.

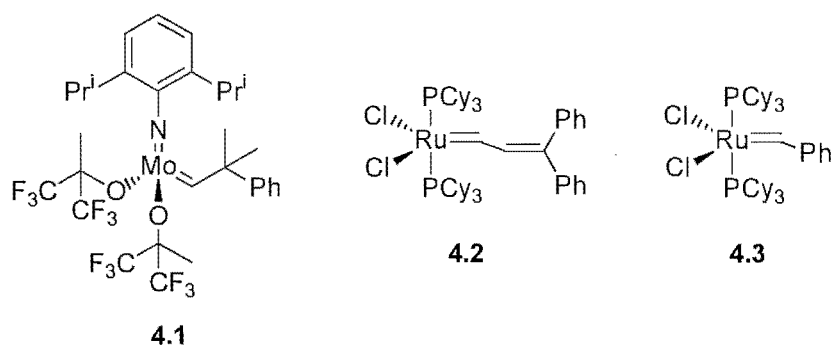


Figure 4.4 Commonly used molybdenum and ruthenium carbenes for RCM.

Hölder and Blechert have reported RCM to form a bicyclic system as part of a concise synthesis of coronafacic acid (**Figure 4.5**).⁹⁹

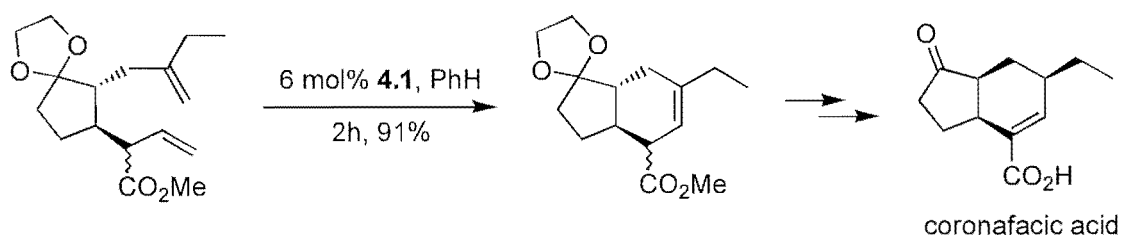


Figure 4.5 The synthesis of coronafacic acid by RCM.

Martin and co-workers have demonstrated the feasibility of RCM for the synthesis of a number of fused bicyclic alkaloid skeletons (**Figure 4.6**).¹⁰⁰ These examples have a nitrogen at one of the bridgeheads. This strategy has been utilized by other groups to synthesize a number of simple alkaloids.¹⁰¹

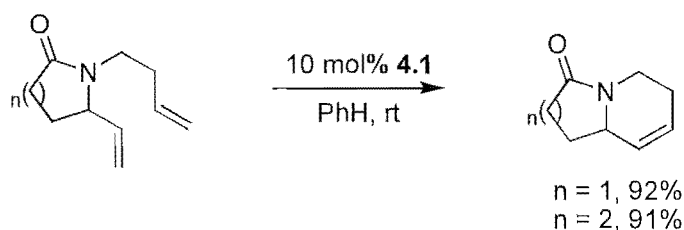


Figure 4.6 Synthesis of bicyclic alkaloid skeletons.

Grubbs and co-workers have recently demonstrated the application of RCM to the syntheses of chromenes¹⁰² and bridged bicyclic compounds (**Figure 4.7**).¹⁰³

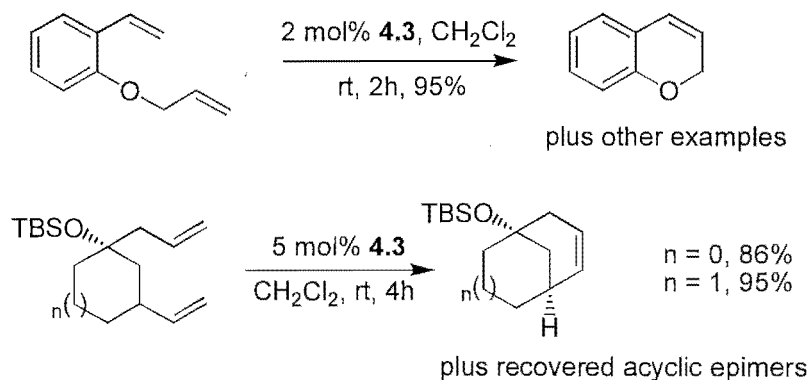


Figure 4.7 Applications of RCM to the synthesis of chromenes and bridged bicyclic compounds.

In a recent report, Jenkins and co-workers have detailed the application of RCM to annelation in the context of carbohydrate synthesis (**Figure 4.8**).

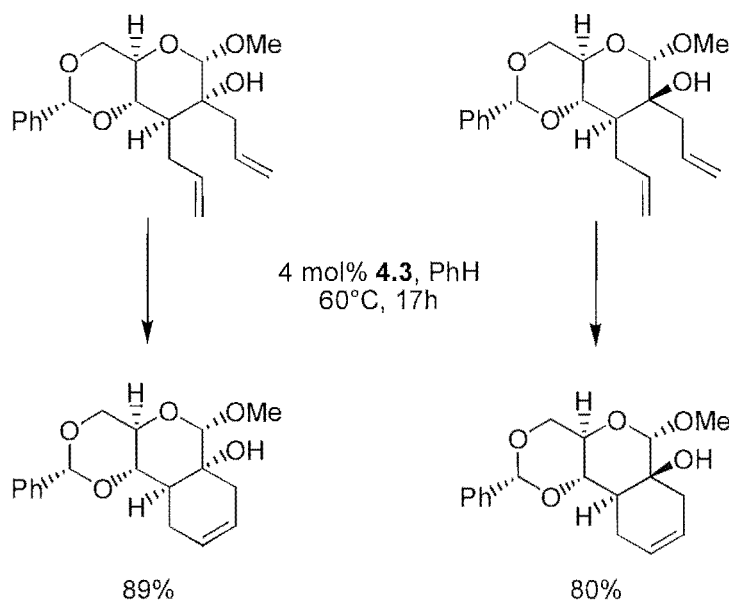
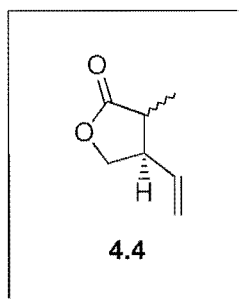


Figure 4.8 Carbohydrate cyclohexene derivatives synthesized by RCM.

These examples demonstrate that there is substantial potential for cyclohexene synthesis by RCM. Most of these systems would be difficult to synthesize by common methods for cyclohexene synthesis (eg, Diels–Alder, Robinson annelation). Although alternate syntheses of these compounds can be conceived, the high versatility and functional group tolerance of Grubbs' catalyst (carbene **4.3**, **Figure 4.4**) means that concise syntheses are possible.

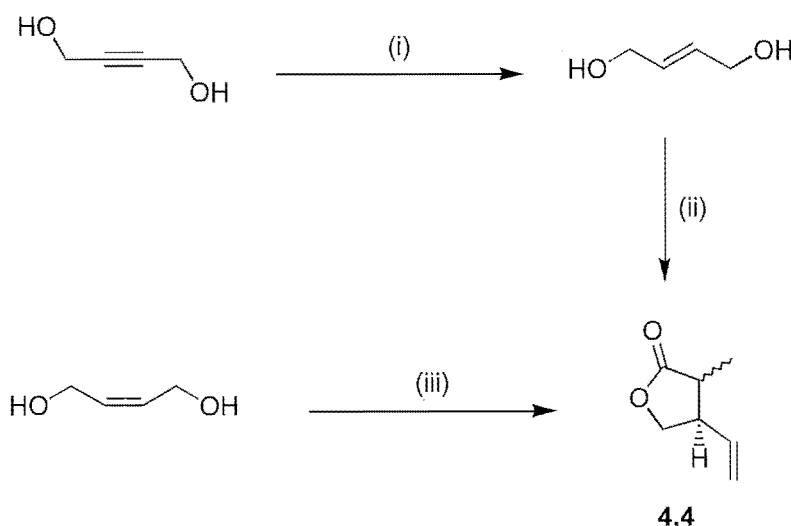
In order to investigate the application of RCM to the synthesis of taxane C-rings, a suitable starting material was required. Tetrahydrofuranone **4.4** was chosen as the compound from which to explore the proposed RCM chemistry. It was selected for two reasons: it contained suitable functionality, and it could be synthesized on a large scale by a two step sequence. There was also some latitude for the intermediates derived from this compound to be elaborated into compounds useful for alternative routes to the taxanes.



4.2 Synthesis of the Acyclic Diene for RCM Studies

Yoshikoshi and co-workers have reported a synthesis of tetrahydrofuranone **4.4** by Johnson–Claisen rearrangement.¹⁰⁴ Although this rearrangement could not be readily applied to the problem of annelation of a C-ring to a taxane AB-ring system,¹⁰⁵ in the context of exploratory studies it was considered unimportant how this first alkene was introduced.

Reduction of butyne-1,4-diol to (*E*)-butene-1,4-diol was achieved on a 20 gram scale with lithium aluminium hydride by the procedure of Zercher and co-workers¹⁰⁶ (Scheme 4.1).[†] Heating this diol at 150 °C for 16 hours, in the presence of triethyl orthopropionate and catalytic hydroquinone, resulted in Johnson–Claisen rearrangement and subsequent lactonization. Fractional distillation of the reaction mixture gave the product **4.4** as a 1.4:1.0 mixture of diastereomers in 70% yield.



Scheme 4.1^a Synthesis of lactone **4.4** by Johnson–Claisen rearrangement.

^a Reagents: (i) LiAlH₄, THF, reflux, 18 h, 80%; (ii) (EtO)₃CHCH₂CH₃, hydroquinone (cat.), 150 °C, 16 h, 70%, dr = 1.4:1; (iii) (EtO)₃CHCH₂CH₃, hydroquinone (cat.), 150 °C, 16 h, < 10%.

[†]

The author would like to thank Dr Jonathan Morris for performing a scale-up of this reaction.

The lack of appreciable diastereoselection in the Johnson–Claisen rearrangement can be accounted for by the lack of stereoselectivity in the formation of the intermediate ketene acetal.¹⁰⁷

Interestingly, when commercially available (*Z*)-butene-1,4-diol was subjected to the same conditions less than 10% conversion of the starting material into product was observed. This lack of reactivity can be explained by consideration of the potential transition structures for the rearrangement (**Figure 4.9**). Neither ketene acetal geometry is able to alleviate the significant interaction between the ketene acetal and the CH₂OH group. The observed reaction can probably be accounted for by the fact that commercial (*Z*)-butene-1,4-diol contains 5-10% (*E*)-butene-1,4-diol.

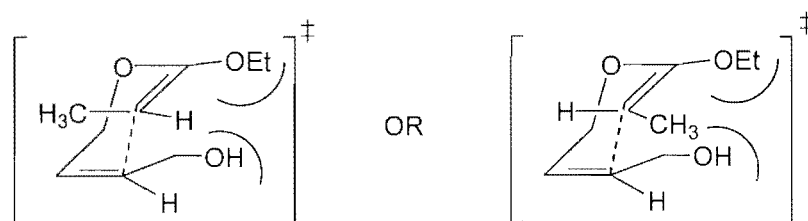
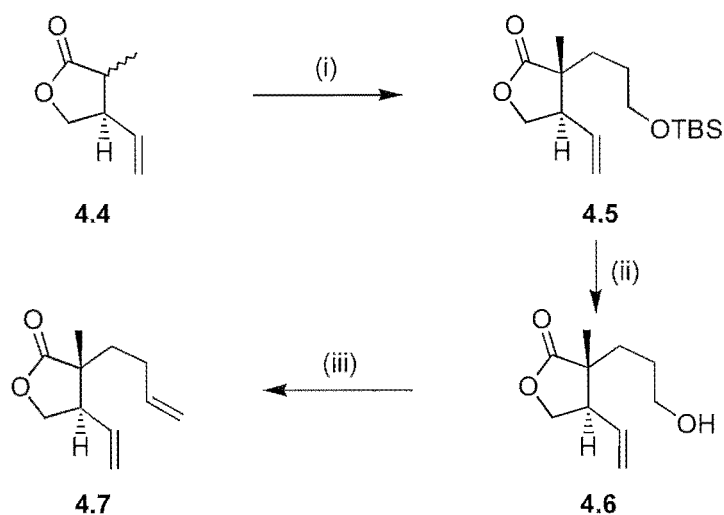


Figure 4.9 Possible chair transition structures for the cyclization of (*Z*)-butene-1,4-diol.

With the furanone **4.4** available in multigram quantities, it was possible to investigate the addition of the second diene. The direct introduction of the desired 3-butenyl system by alkylation of the furanone enolate with homoallyl halides was expected to be problematic, so several alternatives were explored. The first approach was to introduce a three carbon unit as a protected alcohol, then deprotect, oxidize and olefinate (**Scheme 4.2**)



Scheme 4.2^a Synthesis of the diene for RCM studies

^a Reagents: (i) LDA, THF, **4.4**, -78 °C to -20 °C, 1 h, then -78 °C, add DMPU (2 equiv.) then 1-bromo-3-(*tert*-butyldimethylsilyloxy)propane (1.2 equiv.), -78 °C to 25 °C, 14 h, 83%, dr = 3:1 (*trans*:*cis*) (only the major diastereoisomer is shown); (ii) TBAF (2 equiv.), THF, RT, 1 h, *ca* 50%; (iii) (a) DMSO, (COCl)₂, CH₂Cl₂, -78 °C, add **4.6**, -78 °C, 30 min, add Et₃N, -78 °C to 25 °C, 30 min; (b) Ph₃P⁺CH₃Br⁻, *n*-BuLi, THF, 0 °C, 1 h, then -78 °C, add aldehyde, -78 °C to 25 °C, 6 h. 62% for two steps, dr = 3:1 (*trans*:*cis*).

Addition of **4.4** to a solution of lithium diisopropylamide in THF at -78 °C, with subsequent warming to -20 °C over one hour resulted in formation of the desired enolate. This solution was recooled to -78 °C and two equivalents of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU) were added. Addition of 1-bromo-3-(*tert*-butyldimethylsilyloxy)propane and subsequent warming to room temperature over a period of 14 hours gave the desired alkylated furanone **4.5**. The ratio of diastereoisomers was 3:1 based on the integration of the methyl resonances at δ_{H} 1.09 (major diastereomer) and δ_{H} 1.21 (minor diastereomer). A 2D NOESY spectrum failed to confirm which isomer was predominant, although on the basis of much literature precedent it was assumed that the desired *trans*[†] isomer was the major component.¹⁰⁸ This was later confirmed by a 2D NOESY experiment once a bicyclic structure was obtained (*vide infra*).

[†] The descriptors *trans* to *cis* are used as for fused steroidal ring systems and with reference to the ring-junction stereochemistry in the final cyclized compound.

This was later confirmed by a 2D NOESY experiment once a bicyclic structure was obtained (*vide infra*).

Desilylation was achieved by treatment of **4.5** with tetra-*n*-butylammonium fluoride (TBAF) in THF at room temperature for one hour. Flash chromatography of the resultant alcohol was capricious and could only be achieved with any degree of success in solvent systems where the alcohol had an R_f of *ca* 0.5. Under these conditions, the alcohol was isolated in 55% yield, but contained *ca* 10% of unidentified silyl impurities. Use of less polar solvent systems resulted in poor mass balance, indicating decomposition of the product on silica.

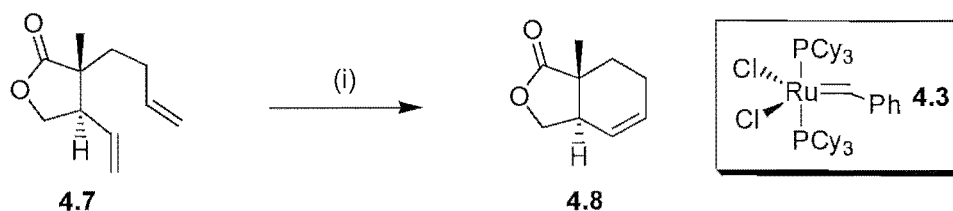
Alcohol **4.6** was subjected to a standard two-step oxidation–olefination procedure. Oxidation of the alcohol by the method of Omura and Swern,¹⁰⁹ was followed by treatment of the aldehyde with methylene triphenylphosphorane in THF at -78 °C with subsequent warming to room temperature. This sequence provided the desired diene **4.7** in two steps in an unoptimized yield of 62%.

4.3 Preliminary RCM Studies

With diene **4.7** available by the above route, it was possible to examine the ring-closure (**Scheme 4.3**). Diene **4.7** was dissolved in *freshly distilled* CH_2Cl_2 that had been degassed by three freeze–pump–thaw cycles. Grubbs' catalyst (**4.3**, 15 mol%), dissolved in a small volume of degassed CH_2Cl_2 was added *via* syringe, and the reaction was heated to reflux under argon. Initial observations were positive with the reaction rapidly changing in color from deep purple to pale yellow.[†] This observation was supported by the appearance of a new compound by TLC after one hour. After heating

[†] This color change is, in general, indicative of loss of the benzylidene group from the catalyst and is consistent with the observations of Grubbs' and co-workers. Grubbs, R. H. Personal communication.

at reflux for a further 13 hours, TLC indicated no starting material to be present so the reaction was cooled to room temperature and the solvent removed *in vacuo*.

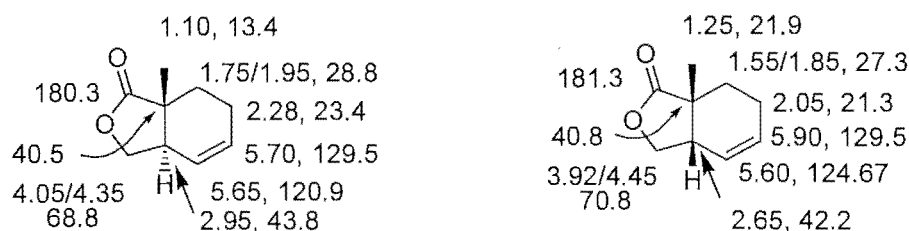


Scheme 4.3^a Formation of the bicyclic lactone by RCM.

^a Reagents: 15 mol% **4.3**, CH_2Cl_2 , reflux, 14 h, 60%, dr *ca* 1.5:1 (the major diastereoisomer is shown). [diene] = 27 mM.

^1H nmr analysis of the crude product indicated that cyclization had occurred. The loss of the resonances due to the terminal alkene hydrogens (δ_{H} 4.90 – 5.40) provided some evidence for this. There were also significant changes in the appearance and multiplicity of many of the other resonances, particularly those for the $-\text{CH}_2\text{O}-$ and $-\text{CHCH}_2\text{O}-$ resonances. A new multiplet was also present centered on *ca* δ_{H} 5.60, a chemical shift typical for alkene protons of cyclohexenes.

A full series of two-dimensional experiments were also conducted to allow conclusive assignment of the ^1H and ^{13}C spectroscopic data, along with complete establishment of the connectivity. The information obtained from the HSQC and HMBC experiments is shown in **Figures 4.10** and **4.11**. A 2D NOESY experiment also demonstrated the stereochemistry across the ring junction of the major isomer to be *trans*.



All data are in the format $\delta_{\text{H}}, \delta_{\text{C}}$

Figure 4.10 HSQC and HMBC-based assignment of chemical shift data for **4.8**.

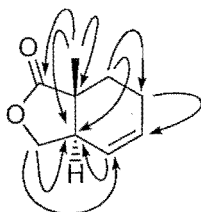


Figure 4.11 Key HMBC correlations for the *trans* diastereoisomer of **4.8**.

Further inspection of the ^1H nmr spectroscopic data provided a surprise: the diastomeric ratio had decreased from *ca* 3:1 to 1.5:1. Whilst an explanation for this observation was not immediately apparent, further experimentation (*vide infra*) provided some insight into the cause of this decrease.

4.4 A Second Generation Route to the RCM Substrate

The first route to the diene described in **Section 4.2** suffered from a number of problems. The most significant problem was the low overall yield of the sequence, and in particular the poor yield of the deprotection step. After screening a number of other reagents [HF, AcOH, $\text{PdCl}_2(\text{MeCN})_2$] for the removal of the *tert*-butyldimethylsilyl group from **4.5** without any promise, it was decided to develop a route that avoided the use of protecting groups.

It was envisaged that two conceptually simple, but related, solutions to the problem might be possible. Both rely on the use of dihalides as alkene equivalents (**Figure 4.12**). Path A calls for monoalkylation of the furanone by a four-carbon dihalide, followed by elimination of the terminal halide. Path B involves the use of a three-carbon dihalide as a surrogate for a carbonyl group that could then be olefinated following the already established transformation.

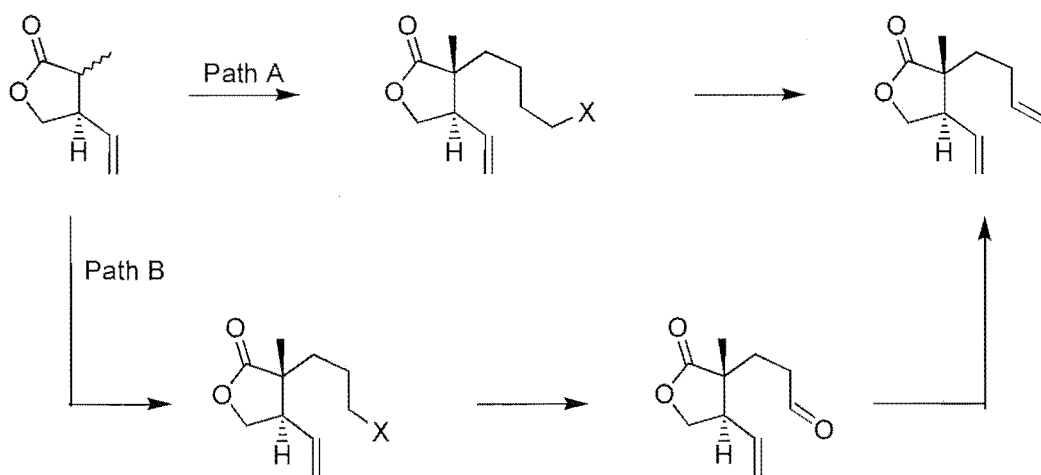
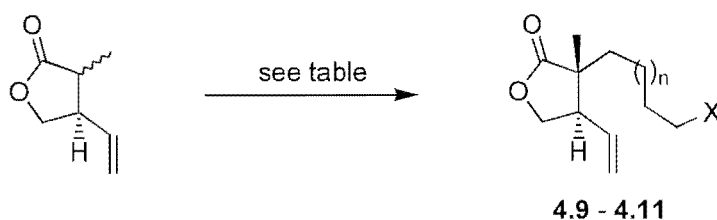


Figure 4.12 The proposed use of dihalides for the introduction of the alkene.
X = Br, I.

It seemed that the significant obstacle to overcome in implementing either of these routes would be the monoalkylation of the furanone. Fortunately, this proved to be straightforward. The furanone could be alkylated by a number of dihalides under essentially the same conditions as previously established (as shown in **Scheme 4.4**). Two minor modifications were made: (i) slightly more electrophile was used (1.5 equivalents instead of 1.2 equivalents), and (ii) in an effort to maximize the diastereoselection, the reactions were typically cooled to -95 °C prior to addition of the electrophile. After workup, the ¹H nmr spectrum of the crude reaction mixtures showed no traces of dialkylated products. It is also of note that no difference in the level of

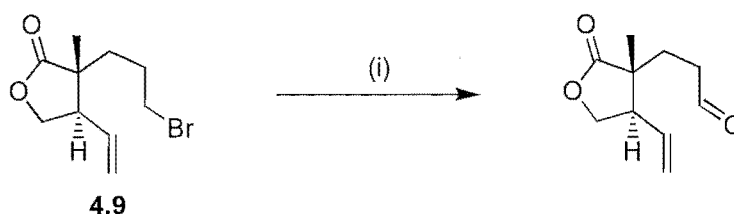
diastereoselection was obtained when the reaction was only cooled to -78 °C before addition of the dihalide (compare entry 3 and entry 4).



n	X	Conditions	Yield and dr [†]
0	Br 4.9	LHMDS, -78 °C to -20 °C then -95 °C, add DMPU (2 equiv.) then halide, -78 °C to 25 °C	71% dr = 3:1
1	I 4.10	LHMDS, -78 °C to -20 °C then -78 °C, add DMPU (2 equiv.) then halide, -78 °C to 25 °C	61% dr = 7:5
1	Br 4.11	LHMDS, -78 °C to -20 °C then -78 °C, add DMPU (2 equiv.) then halide, -78 °C to 25 °C	74% dr = 3:1
1	Br 4.11	LHMDS, -78 °C to -20 °C then -95 °C, add DMPU (2 equiv.) then halide, -78 °C to 25 °C	76% dr = 3:1

Scheme 4.4 Alkylation of furanone **4.2** with dihalides. [†] Ratio of *trans* to *cis*.

With compound **4.9** in hand it was possible to investigate the Kornblum oxidation of the bromide (**Scheme 4.5**).¹¹⁰ To this end, bromide **4.9** and one equivalent of silver tetrafluoroborate were stirred at room temperature for 17 hours in DMSO. Triethylamine was then added and the reaction stirred for 30 minutes at room temperature. After standard aqueous workup, the crude reaction mixture was analyzed by ¹H nmr. Although two diastereomeric aldehydes had been formed, a substantial amount of starting material (*ca* 30%) remained.



Scheme 4.5^a Kornblum oxidation of bromide **4.9** with AgBF₄/DMSO/Et₃N.

^a Reagents: AgBF₄ (1 or 2 equivalents), DMSO, 25 °C, 17 h, then Et₃N, 25 °C, 30 min, 2.5:1 product:starting material (by ¹H nmr). Yield not determined.

In an effort to force this reaction to completion, bromide **4.9** was treated with two equivalents of silver tetrafluoroborate under the same conditions. This reaction gave an almost identical result to the first reaction. This avenue was not pursued any further.

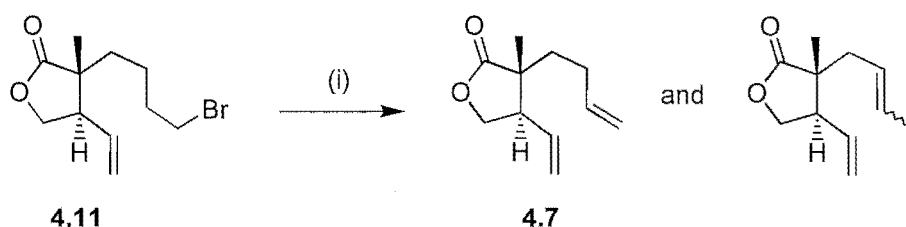
The elimination of bromide **4.11** was investigated as an alternative to the Kornblum oxidation of **4.9**. The E2 elimination of the halide proved to be very slow. For example, treatment of this compound with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1-10 equivalents) at various temperatures from room temperature to 60 °C in benzene gave only 10-15% conversion after periods of up to 24 hours. Although a number of alternative methods exist for the elimination of terminal bromides (eg, KOBu^t, KOH, lithio alkylamides) related studies had suggested that none of these would be effective here.¹¹¹

An attempt to effect the elimination by the use of an iodine as leaving group was also made. However, when terminal iodide **4.10** was treated with DBU in benzene at 60 °C for 12 hours, the majority of the products were water-soluble. This would seem to indicate that alkylation was the predominant pathway for iodide **4.10**.

A search of the literature for alternative methods revealed a little cited 1986 communication by Jeropoulos and Smith describing the elimination of alkyl halides with stoichiometric low-valent nickel complexes and DBU.¹¹² A major drawback of this method seemed to be the propensity of terminal alkenes to isomerize under nickel catalysis after elimination. Despite this problem, this method was investigated because: (i) it seemed likely to yield the desired compound in a single step under mild conditions, and (ii) it was reasoned that alkene isomerization could possibly be suppressed by manipulation of the reaction conditions or possibly by the use of different ligands.

In the initial reaction, *n*-butyllithium (2 equivalents) was added to a suspension of *freshly prepared* dichlorobis(triphenylphosphine) nickel(II) (one equivalent) and triphenylphosphine (2 equivalents) in freshly distilled THF (degassed by three freeze–pump–thaw cycles) at room temperature. After stirring the resultant deep red solution briefly, the bromide **4.11** (one equivalent) and DBU (2 equivalents) were added. The reaction was allowed to stir at room temperature for 12 hours. After aqueous workup, an oily crystalline solid was obtained.

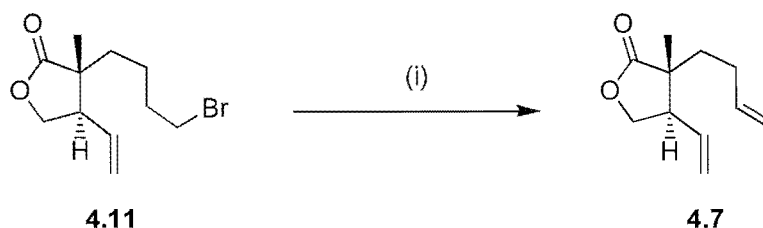
¹H nmr analysis of this solid showed that the desired reaction had occurred (**Scheme 4.5**). The presence of the product was readily confirmed by comparison of the spectrum with that for an authentic sample of **4.7** synthesized previously. However, the product was contaminated by triphenylphosphine and internal alkene isomers (diagnostic signals included multiplets at δ_{H} 5.30 - 5.60). Flash chromatography gave the desired compound in 83% total yield including *ca* 15% of the alkene isomers.



Scheme 4.5 Initial conditions for the low-valent Ni mediated elimination of bromide **4.11**.

^a Reagents: (i) $\text{NiCl}_2(\text{PPh}_3)_2$, *n*-BuLi (2 equiv.), PPh_3 (2 equiv.), THF, 25 °C, then add **4.11** and DBU (2 equiv.), 25 °C, 12 h, 83%, 6:1 **4.7**:alkene isomers.

After careful consideration of the experimental procedure reported, it was decided to perform the reaction at a lower temperature than described by the authors. It was hoped that this would suppress alkene isomerization, but still allow the oxidative addition and elimination steps to occur. Thus treatment of the bromide **4.11** with the same reagents at 0 °C for one hour, followed by stirring at room temperature for 2.5 hours, resulted in the clean transformation of starting material into product (as evidenced by TLC). After workup and flash chromatography, **4.7** was obtained in 57% yield (**Scheme 4.6**). There was no indication of isomeric alkenes by ^1H nmr. Numerous repeats of this reaction gave comparable yields.



Scheme 4.6 Conditions for the low-valent Ni mediated elimination of bromide **4.11** without double bond isomerization.

^a Reagents: (i) $\text{NiCl}_2(\text{PPh}_3)_2$, *n*-BuLi (2 equiv.), PPh_3 (2 equiv.), THF, 0 °C, then add **4.11** and DBU (2 equiv.), 0 °C, 1 h, then 25 °C, 2.5 h, 57%.

4.5 Further RCM Studies

The establishment of a concise and reliable route to diene **4.7** made it possible to further investigate the RCM reaction. However, initial attempts to replicate the earlier result indicated that the reaction was very capricious. For example, treatment of diene **4.7** with Grubbs' catalyst under the same conditions as established in **Section 4.3** yielded predominantly starting material. Closer inspection of the ^1H nmr spectrum lead to the conclusion that the minor *cis* diene diastereoisomer was being consumed rapidly, leaving behind the *trans* diastereoisomer.

When prolonged reaction times (> 12 hours) were employed, substantial darkening of the reaction mixture occurred. This was presumably due to polymer formation, and several observation supported this presumption. Under these conditions, the resonance belonging to the $-\underline{\text{CH}}\text{CH}_2\text{O}-$ proton for the *trans* diene diastereoisomer (δ_{H} 3.05) became broader and diminished in intensity. There were also changes in the multiplicity of resonances in the alkene region of the spectrum (δ_{H} 4.90 – 5.30 and δ_{H} 5.50 – 5.80). Broadening of these resonances was also observed. Mass spectrometry also indicated the presence of a number of high molecular mass compounds in the reaction mixtures.

These observations imply a process whereby one diastereoisomer (the minor *cis* isomer) was being cyclized rapidly whilst the major *trans* diastereoisomer was being slowly polymerized rather than cyclized. A working hypothesis for this is presented in **Figure 4.13**.

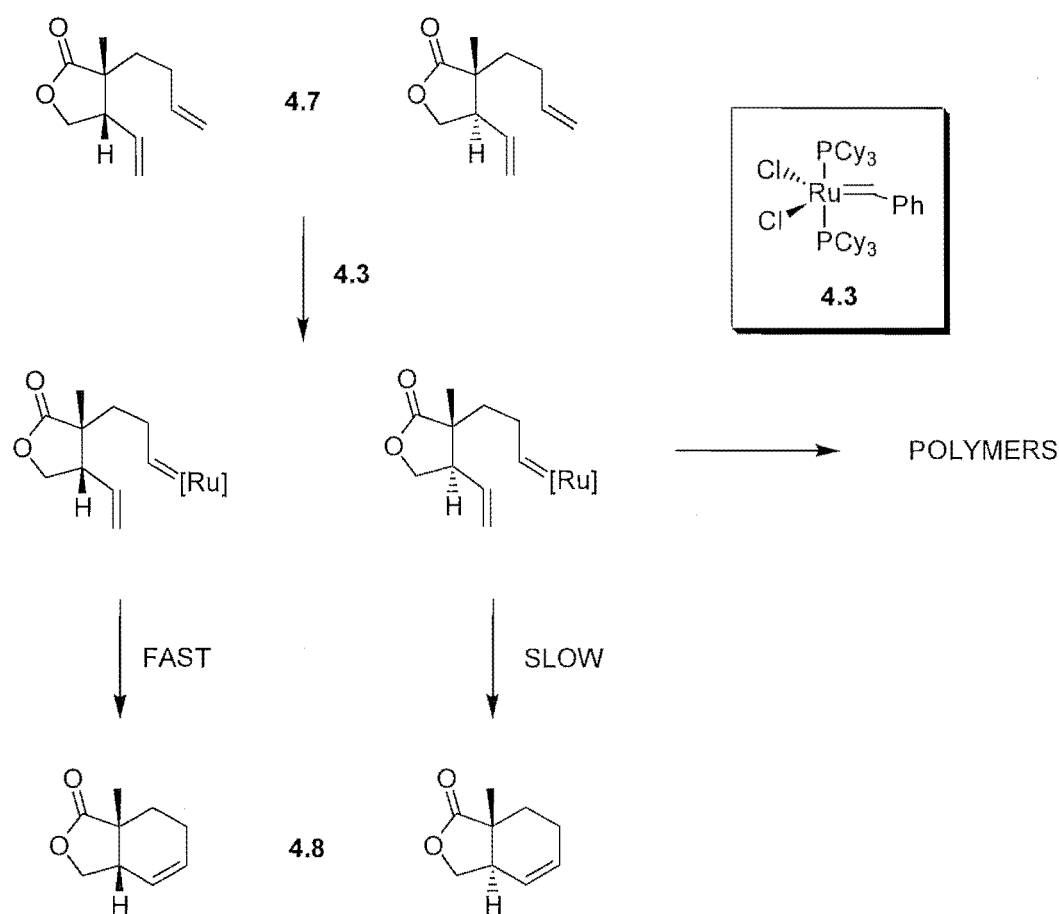


Figure 4.13 A hypothesis for the observations made with respect to the RCM of diastereoisomers of **4.7**.

Based on this hypothesis, it was reasoned that two changes to the experimental procedure might result in more consistent cyclization results. Firstly, the use of more dilute reaction conditions should help favor *intramolecular* coordination of the second alkene over *intermolecular* processes. This should help decrease problems with polymerization. Second, the addition of copper(I) chloride, which is known to complex phosphines and increase the rate of RCM reactions,¹¹³ might also favor the desired process if the reaction was also conducted at reasonable dilution.

Based on this reasoning, the reaction was first conducted under more dilute conditions. Thus, diene **4.7** was heated at reflux in CH_2Cl_2 for 16 hours with a diene concentration of 10 mM (*cf.* the original concentration of 27 mM) along with Grubbs' catalyst (**4.3**, 10

mol%). This resulted only in the cyclization of the *cis* isomer, with the *trans* isomer remaining uncyclized. Gratifyingly, there was no apparent problem with polymerization.

The addition of 10 equivalents copper(I) chloride to a reaction performed under the same conditions (reflux in CH₂Cl₂ for 16 hours with a diene concentration of 10 mM, 10 mol% Grubbs' catalyst) resulted only in the cyclization of the *cis* isomer, with the *trans* isomer remaining uncyclized. The effect of copper(I) chloride on the RCM reaction rate was clearly not sufficient to cause cyclization of the *trans* isomer within this time period.

With the problem of polymerization solved, it was possible to increase the temperature at which the reaction was conducted. Although the rates of both reactions are likely to be increased by raising the temperature,[†] it was fully expected that more dilute reaction conditions would suppress the rate of polymerization.

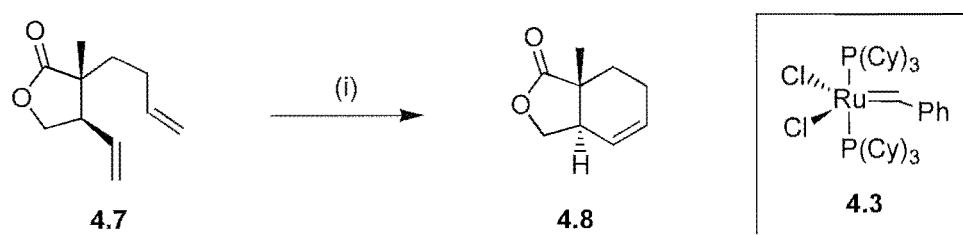
The results of reactions conducted at higher temperature were positive. In the initial experiment, Grubbs' catalyst (20 mol%)[‡] in a small volume of *freshly distilled and degassed* benzene was added to solution of **4.7** in *freshly distilled and degassed benzene* at reflux. The diene concentration was 10 mM. The reaction was carefully monitored by the removal of 50 μ L aliquots that were evaporated to dryness and analyzed by ¹H nmr. The reaction was easily followed by the disappearance of the resonances belonging to the –CHCH₂O– protons (*trans* diastereoisomer δ_{H} 3.05; *cis* diastereoisomer δ_{H} 2.95). Analysis at one hour by ¹H nmr showed that reaction was occurring and significantly that the *trans* diastereoisomer was also being cyclized. After 4.5 hours the

[†] However, the *relative* difference in the rates of the two reactions may also vary depending on the temperature dependence of each reaction rate.

[‡] Additional catalyst was used due to the decomposition of the catalyst at higher temperatures.

reaction was stopped by cooling to room temperature and removing the solvent. Flash chromatography of the residue gave the cyclized product **4.8** as a 2.6:1 (*trans*:*cis*) mixture of diastereoisomers in 68% yield. A small amount (15%) of uncyclized *trans* diene was also obtained.

This result clearly indicated that the problems encountered could be overcome by using more dilute reaction conditions and higher temperature. After a considerable amount of experimentation, it was discovered that the optimal conditions were to use 20 mol% of Grubbs' catalyst, with a diene concentration of 10 mM in benzene at reflux for 4.5 hours. This procedure gave reliable yields of *ca* 65% and acceptable diastereomeric ratios of 2.2-2.6:1 (**Scheme 4.6**).



Scheme 4.7^a Optimized conditions for the RCM of diene **4.7**.

^a Reagents: (i) Addition of 20 mol% **4.3** to diene **4.7** in PhH at reflux, 4.5 h, 62-68%, dr 2.2-2.6:1 (*trans*:*cis*, the major *trans* diastereoisomer is shown). [diene] = 10 mM.

It was also observed that the use of > 20mol% of catalyst resulted in rapid reaction (< one hour with 40 mol%) but this was considered unnecessary for the task at hand. It does however suggest that for more difficult cyclizations the use of higher catalyst loading at increased temperature may well be advisable.

It is possible to speculate as to potential reasons for the differences in rates of cyclization based on the mechanism proposed by Grubbs and co-workers for the reaction of diethyldiallylmalonate with dichlorobis(tricyclohexylphosphine)methylidene ruthenium (IV). The two structures shown below in **Figure 4.14** were considered to be likely reaction intermediates *en route* to the desired cyclohexene.¹¹⁴

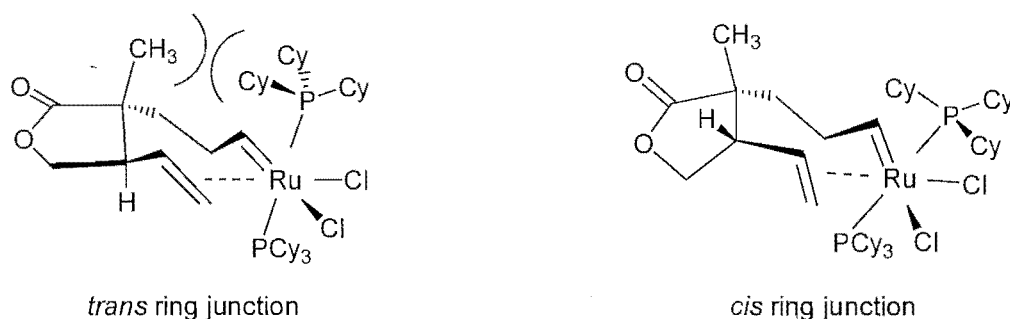


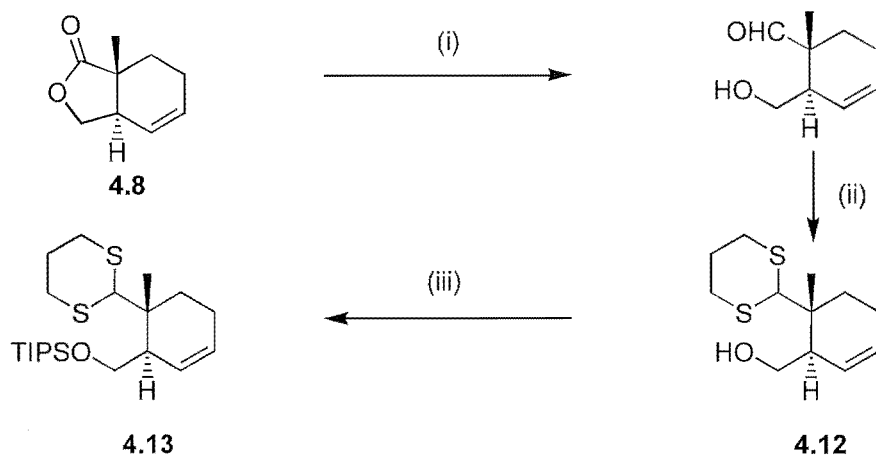
Figure 4.14 Probable intermediates in the RCM reaction.

Inspection of these models reveals some potential problems with respect to the spatial proximity of various groups. For the *trans* diastereoisomer, one of the tricyclohexylphosphine ligands is proximal to the methyl group of the lactone when the second alkene is coordinated to the ruthenium alkylidene formed by initial metathesis of the but-3-enyl side chain. This interaction is alleviated somewhat in the *cis* diastereoisomer. With this diastereoisomer the stereochemistry at the ring junction allows the coordination of the second alkene without such significant transannular interactions.

4.6 Dithiane Synthesis from the RCM Product

Although the aim of these model studies was to evaluate the usefulness of RCM for the introduction of taxane C-rings, lactone **4.8** could potentially be transformed into a useful C-ring building block for alternative approaches to the taxanes.

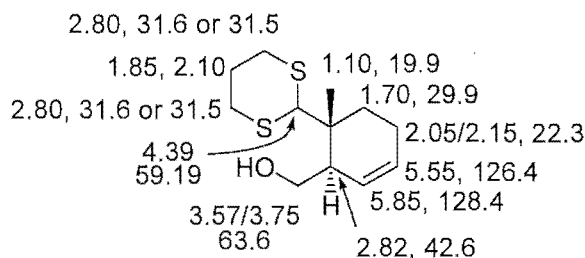
To this end, the sequence of transformations shown in **Scheme 4.8** was performed. The lactone was reduced with diisobutylaluminium hydride (DIBAL-H) in toluene at low temperature. Although a lactol had been expected as the product of this reaction, the ^1H nmr spectrum of the crude product showed the presence of a single aldehyde, along with starting material and some fully reduced diol. On the basis of integrals of the CH_3 resonances, it appeared that fortuitously the *cis* isomer of the lactone had been fully reduced. The crude product was dissolved in CH_2Cl_2 , cooled to $0\text{ }^\circ\text{C}$, and was treated with boron trifluoride diethyl etherate and propane-1,3-dithiol. The reaction was stirred at $0\text{ }^\circ\text{C}$ to $25\text{ }^\circ\text{C}$ for a period of two hours at which point ^1H nmr analysis showed the aldehyde to be absent. Standard aqueous workup, followed by purification of the crude product by flash chromatography, gave the dithiane **4.12** (68% based on returned starting material) as a single diastereoisomer.



Scheme 4.7^a Transformation of the lactone **4.8** into dithianes.

^a Reagents: (i) DIBAL-H, PhMe, -78°C , 1.5 h; (ii) propane-1,3-dithiol, $\text{BF}_3\cdot\text{OEt}_2$, CH_2Cl_2 , 0°C , 3 h, 68% based on returned starting material (over two steps); (iii) TIPSOTf (1.1 equiv.), 2,6-lutidine (2 equiv.), CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 16 h, 100%.

A full range of two-dimensional nmr experiments were performed on **4.12**, confirming the molecular connectivity and allowing assignment of the ^1H and ^{13}C nmr data. The information obtained from the HSQC and HMBC experiments is shown in **Figures 4.15** and **4.16**.



All data are in the format $\delta_{\text{H}}, \delta_{\text{C}}$

Figure 4.15 HSQC and HMBC-based assignment of chemical shift data for **4.12**.

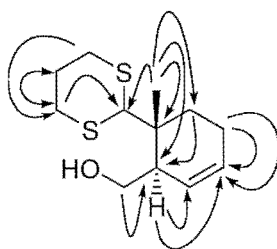


Figure 4.16 Key HMBC correlations for **4.12**.

The dithiane could be readily protected by triisopropyl triflate under standard conditions to give silyl ether **4.13**. The potential use of compounds of this type for other approaches to taxane synthesis are discussed in **Chapter 6**.

4.7 Summary

The synthesis of bicyclic lactone **4.8** by ring-closing metathesis (RCM) has been described.

Investigation of this reaction has indicated that for fused bicyclic systems, there may be different pathways for diastereoisomers. In particular, it was observed that acyclic lactone precursors with a *cis* ring junction were readily cyclized whereas those compounds with a *trans* ring junction were only cyclized readily at higher temperatures and under relatively dilute conditions

Optimal conditions for the synthesis of **4.8** involved the addition of 20 mol% Grubbs' catalyst to a solution of the acyclic precursor *in benzene that was already at reflux*. Reaction under these conditions produced **4.8** in 62-68% yields with diastereomeric ratios of 2.2-2.6:1 (*trans:cis*).

A possible rationale for the differences in reactivity has been presented. However, a clearer understanding of the reasons for the capricious nature of the reaction will require further investigation.

These investigations have demonstrated the potential use of ring-closing metathesis for the formation of taxane C-rings. In particular, the strategy described has the advantages of not requiring protecting groups, and it places the double bond in an appropriate position that should allow for facile elaboration into the oxygenation patterns found in the natural taxanes.

Bicyclic lactone **4.8** could also be elaborated into a protected dithiane that may be of value to alternative taxane synthesis strategies.

Chapter Five

The Intramolecular Diels–Alder Synthesis of Bicyclo[4.3.1]decanes

5.1 Introduction

The lack of success of the ring-closing metathesis approach to the desired bicyclo[5.3.1]undecane systems described in **Chapter 3** lead to the need for an alternative route to these compounds. One such approach involves the use of intramolecular Diels–Alder methodology.

The [4 + 2] cycloaddition of dienes and alkenes was initially observed by Albrecht in 1906.¹¹⁵ However, it was not until 1928 that Diels and Alder reported the reaction of several dienes and alkenes in the seminal study that defined the *Diels–Alder* reaction (**Figure 5.1**).¹¹⁶

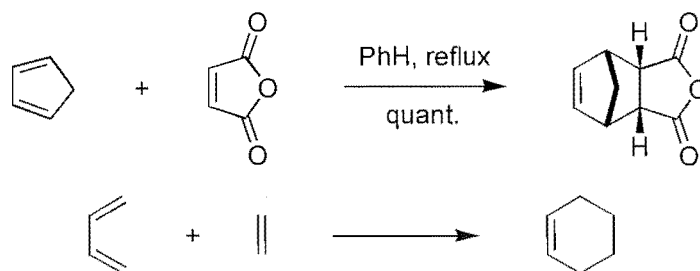


Figure 5.1 The reaction of cyclopentadiene and maleic anhydride, first reported by Diels and Alder in 1928, and the general process for a Diels–Alder reaction.

The Diels–Alder reaction has been widely employed in the synthesis of natural products because of its ability to greatly increase molecular complexity.¹¹⁷ At a strategic level, it

is a powerful reaction to employ as the key step in a synthesis.¹¹⁸ This is because it allows for the formation of up to four stereogenic centers, as well as forming two new carbon-carbon bonds. It is for this reason that much recent research has focussed on developing enantioselective catalysts for the Diels-Alder reaction. Two examples that illustrate the use of the Diels-Alder reaction in natural product synthesis are shown in **Figure 5.2**.

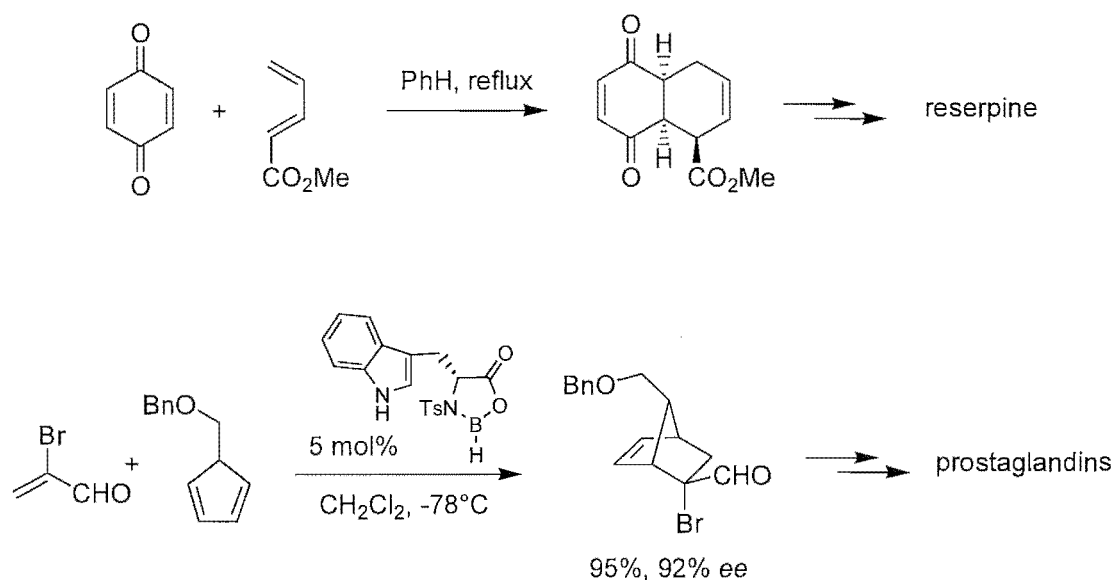


Figure 5.2 The intermolecular Diels-Alder reaction in the synthesis of natural products: (i) Woodward's synthesis of reserpine,¹¹⁹ and (ii) Corey's asymmetric 3rd generation synthesis of prostaglandins.¹²⁰

The use of the Diels-Alder reaction in an *intramolecular* fashion was first reported in 1963.¹²¹ Since that time the intramolecular Diels-Alder (IMDA) reaction has been used to great effect in natural products synthesis (see **Figure 5.3** for two examples).¹²² These reactions are described as *type I* (attachment at C1) or *type II* (attachment at C2), depending on the position of the attachment of the dienophile to the diene (**Figure 5.4**). The majority of examples in the literature are type I IMDA reactions.

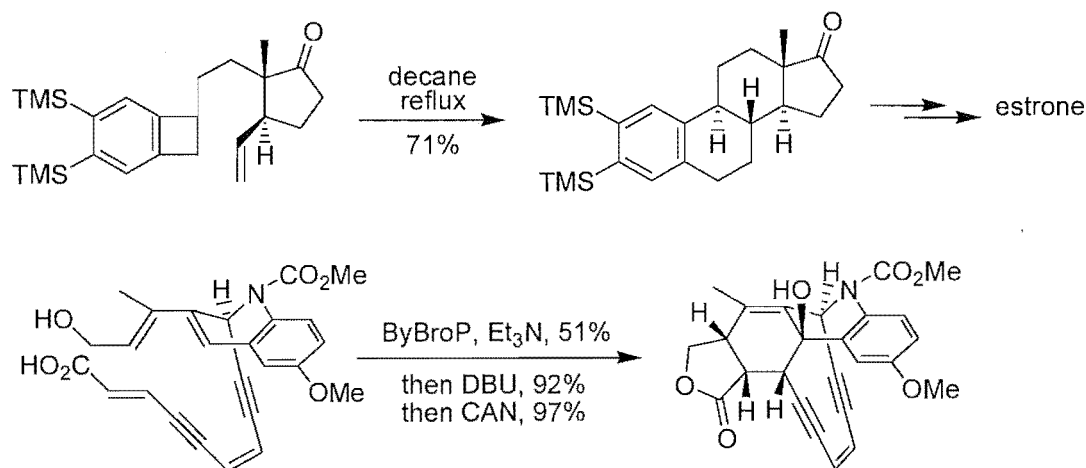


Figure 5.3 The intramolecular Diels–Alder reaction: (i) Vollhardt's synthesis of estrone,¹²³ and (ii) Schreiber's IMDA reaction *en route* to various methylated dynemicins.¹²⁴

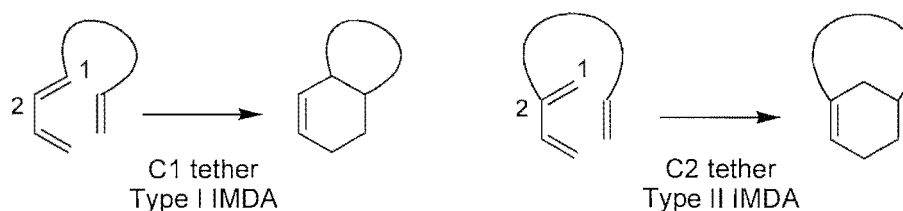


Figure 5.4 Type I and type II IMDA reactions.

Although approaches to the taxanes utilizing the IMDA reaction have been described, they have suffered from a number of problems such as rearrangements, unexpected stereochemistry or difficulties with functionalization of the Diels–Alder adducts (see **Section 1.4.1** for more detail). The major question to be answered before these approaches can be applied to the synthesis of naturally occurring taxanes is that of the relative timing of introduction of functionality. In the author's opinion, it is clear that a compromise must be reached between the potential advantages of heavily functionalized IMDA substrates, and the difficulties involved in functionalization of simple systems. Several examples in **Section 1.4.1** have shown that heavily

functionalized substrates can yield anomalous results and simpler IMDA substrates may not contain sufficient functionality to allow syntheses to be readily completed. The work described in this chapter represents an attempt to reach this compromise.

For reasons that are unclear, it was not possible to synthesize the desired taxane AB-ring system by ring-closing metathesis (as described in **Chapter 3**). It was envisaged that the IMDA reaction might provide an avenue to constructs of the desired type. An overview of this thinking is provided in **Figure 5.5**.

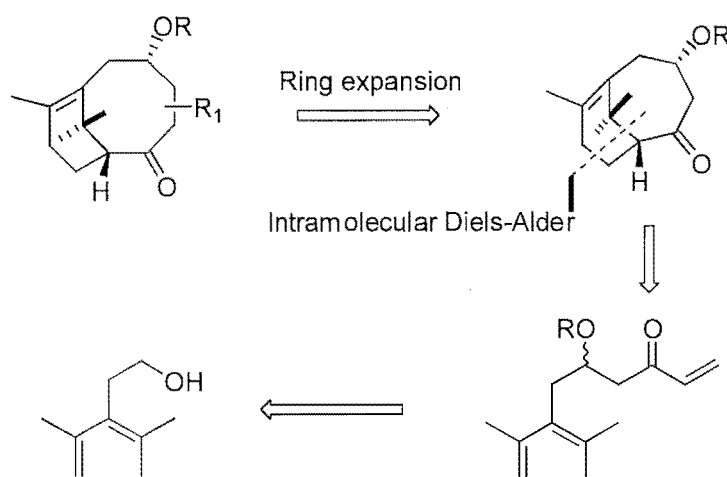


Figure 5.5 A potential route to taxane AB-rings *via* IMDA reaction to give bicyclo[4.3.1]decanes.

Although these constructs are missing one carbon in the B-ring it was felt that they were useful targets because: (a) they could be synthesized readily from compounds described in **Chapter 2**, (b) they had sufficient functionality to allow some latitude for a possible one-carbon ring expansion¹²⁵ (**Figure 5.6**), and (c) they appeared to have sufficient functionality to allow advancement toward the naturally occurring taxanes.

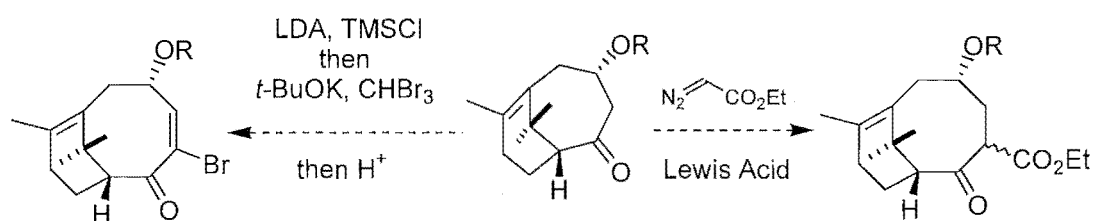


Figure 5.6 Two possible methods for the regioselective ring expansion of bicyclo[4.3.1]decanes.

There is some literature precedent for these plans. For example, Danheiser and co-workers have reported the one carbon expansion of a seven-membered ring *via* dihalocyclopropane cleavage as part of a synthesis of anatoxin (**Figure 5.7**).¹²⁶ Expansions of seven-membered rings using diazo compounds to give cyclooctanes are also known.¹²⁷ An example of this, from Rigby and Senanayake's synthesis of the ophiobolane ring system,¹²⁸ is shown in **Figure 5.7**.

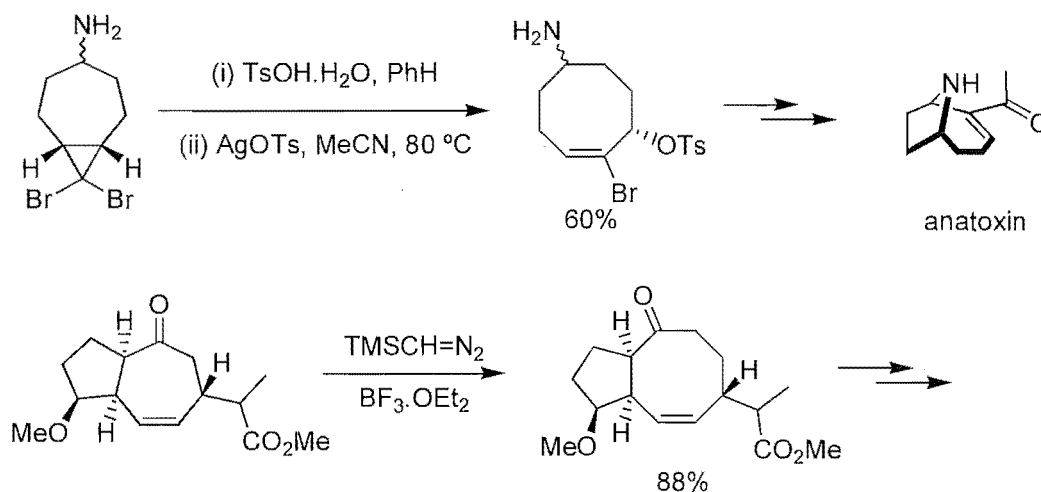


Figure 5.7 Ring expansions in the synthesis of cyclooctanoid natural products.

5.2 Synthesis of the IMDA Substrate

The initial target of these studies was the IMDA substrate **5.5**. A number of possible routes to this compound were considered, and some of the possibilities are shown in **Figure 5.8**.

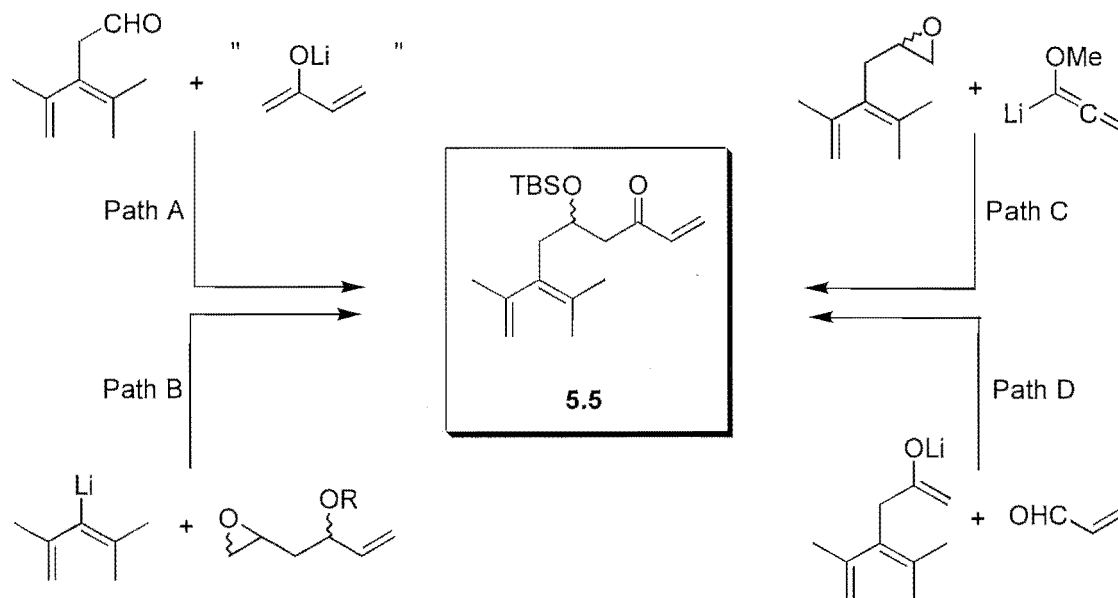
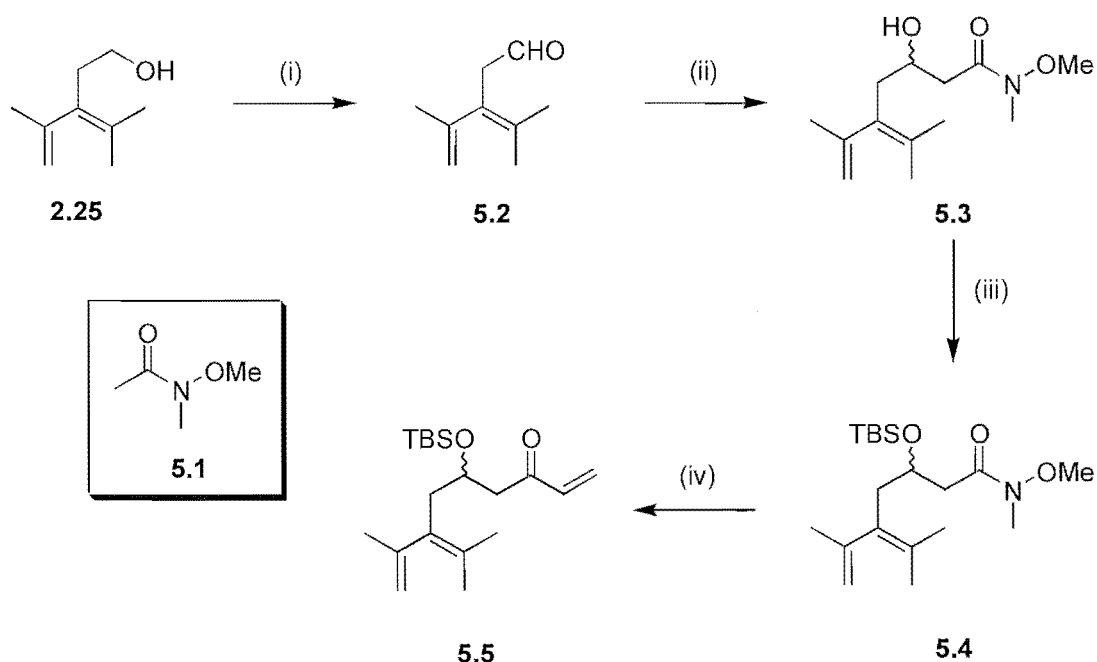


Figure 5.8 Some possible routes to IMDA substrate **5.5**.

Given the ease of synthesis of the diene substructure *via* the dihalocyclopropane cleavage described in **Section 2.3**, all of the potential routes considered were based around the use of an intact diene unit. Path B and path D were quickly ruled out as they appeared likely to require substantial manipulation of protecting groups. Of the two remaining routes, path A was selected because the required aldehyde could be synthesized from alcohol **2.25**. Further, although it required the non-trivial introduction of the enolate of methyl vinyl ketone or an equivalent, this prospect was considered more likely to succeed than the alternative (path D) which required the use of lithiated methoxyallene. The latter compound and its reaction with electrophiles have been described. However, it was not clear from the literature that the required protecting group manipulations would be possible.

The synthetic route that was eventually employed for the synthesis of substrates for the IMDA reaction is shown in **Scheme 5.1**

After surveying several conditions it was discovered that diene alcohol **2.25** was smoothly oxidized to the desired aldehyde **5.2** under conditions similar to those originally described by Omura and Swern.¹²⁹ Dess–Martin periodinane¹³⁰ and tetra-*n*-propylammonium perruthenate (TPAP)¹³¹ proved less effective for this transformation (*ca* 60% and 0% respectively). The crude aldehyde that was obtained proved somewhat unstable, and was best used immediately.



Scheme 5.1^a The synthesis of substrates for the IMDA reaction.

^a Reagents: (i) DMSO, (COCl)₂, CH₂Cl₂, -78 °C, add **2.25**, -78 °C, 30 min, add Et₃N, -78 °C to 25 °C, 30 min; (ii) LDA, THF, **5.1**, -78 °C, 15 min, add **5.2**, -78 °C, 30 min; (iii) TBSCl, DMF, imidazole, 25 °C, 15 h, 57% for three steps; (iv) vinylmagnesium bromide (2.5 equiv.), THF, reflux, 1 h, 56%.

The problem of introducing the enone *via* what amounts to the formal addition of the enolate of methyl vinyl ketone was solved by a three step sequence. This sequence [Scheme 5.1, steps (ii) to (iv)] utilized enolate chemistry and the well known electrophilic properties of Weinreb amides.¹³² A similar reaction sequence has been reported by Palomo and co-workers.¹³³

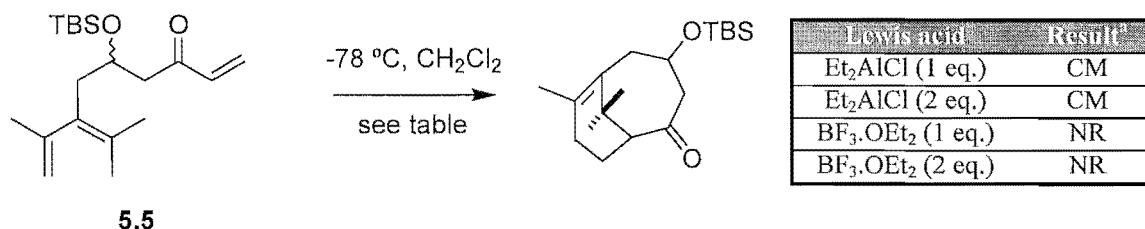
N-Methoxy-*N*-methylacetamide **5.1** was deprotonated by treatment with lithium diisopropylamide in THF at -78 °C. Addition of aldehyde **5.2** to the resulting enolate at -78 °C, followed by stirring at the same temperature, gave the crude aldol adduct **5.3** after workup. The crude aldol adduct was protected with *tert*-butyldimethylsilylchloride under standard conditions.¹³⁴ This sequence gave the desired protected aldol adduct **5.4** in a yield of 56% for the three steps based on the aldehyde after purification by flash chromatography.

With the aldol adduct **5.4** in hand it was possible to investigate the addition of vinyl magnesium bromide to the Weinreb amide. In their original paper, Nahm and Weinreb report that the addition of Grignard reagents to *N*-methoxy-*N*-methylamides occurs in THF at reflux.¹³⁵ In accord with this, the addition of an excess of vinyl magnesium bromide (2.5 equivalents) to a solution of the aldol adduct **5.4** at reflux gave, after workup, the expected enone **5.5**. This result was gratifying, given some concern over the stability of the adduct in THF at reflux, and the potential for Michael-type additions to the enone in the presence of excess vinylmagnesium bromide. The crude product of the reaction was greater than 95% pure by ¹H nmr analysis, but could be further purified by rapid chromatography on silica. This gave analytically pure **5.5** in 56% yield. Efforts to increase the modest yield of this reaction proved fruitless. An alternative reduction–addition–oxidation sequence (lithium aluminium hydride, vinylmagnesium bromide addition, Swern oxidation) was also briefly investigated but failed to give **5.5** in higher yield.

5.3 The IMDA Reaction

5.3.1 Initial Studies: Double-Bond Isomerized Products

The initial studies of the IMDA reaction are shown in **Scheme 5.2**. The conditions selected for these initial attempts were based on the literature and the results obtained in **Chapter 2**.



Scheme 5.2 Initial IMDA studies.

^a NR = no reaction. CM = complex mixture.

Exposure of diene **5.5** to diethylaluminium chloride (one or two equivalents) in CH₂Cl₂ at -78°C proved ineffective, with complex mixtures being isolated. Similarly, treatment of **5.5** with either one or two equivalents of boron trifluoride diethyl etherate in CH₂Cl₂ at -78°C also failed to yield the desired Diels–Alder adduct.

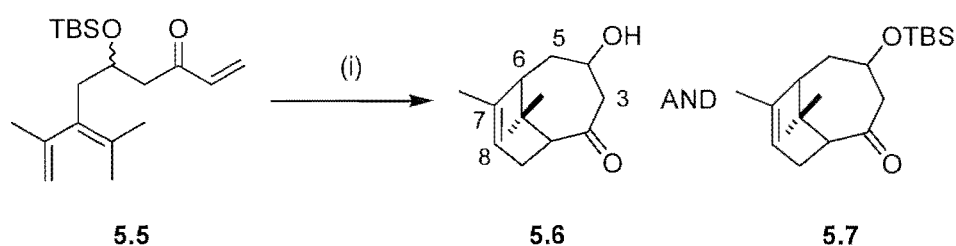
However, treatment of the diene with one equivalent of boron trifluoride diethyl etherate in CH₂Cl₂ at 0°C for 30 minutes resulted in transformation of starting material into two new compounds as indicated by thin-layer chromatography (TLC). After standard aqueous workup, and purification by flash chromatography on silica, two closely related compounds were obtained.

Initial inspection of the ¹H nmr spectra of these compounds indicated that they differed only by the presence of a *tert*-butyldimethylsilyl group. This was confirmed by mass spectrometry. The ¹H nmr spectra clearly showed that the diagnostic resonances for the enone of the starting material (δ_{H} 5.81 (dd), 6.19 (dd), and 6.33 (dd)) were absent,

confirming that a reaction had taken place. An upfield shift ($\Delta\delta_{\text{H}}$ ca 0.65) of the resonances due to the *geminal* vinyl methyls to a chemical shift indicative of a saturated hydrocarbon system (from δ_{H} 1.70 in **5.5** to δ_{H} ca 1.00 and δ_{H} 1.10) was also observed. These observations were encouraging.

Although it seemed unlikely that anything other than the desired Diels–Alder reaction would have occurred under the reaction conditions, further inspection of the ^1H nmr spectrum of the desilylated compound revealed two disconcerting features. The first was a resonance integrating for one proton at δ_{H} 5.47. No resonance would be expected in this region for the desired product, since this chemical shift is typical for a hydrogen attached to a substituted alkene. The second feature was the unexpected multiplicity of the signals in the vinyl methylene region of the spectrum. Although not first order, the signals that probably belonged to H5/H5' were clearly not the expected doublet of doublets. Although there is some possibility of $^4J_{\text{CH}}$ coupling in a cyclic system of this type, the coupling constants were inconsistent with this possibility. Clearly, further analysis was required in order to establish the structure of these compounds.

A full range of two-dimensional nmr experiments were performed on the free alcohol obtained by chromatography. The results of these experiments lead to the conclusion that, although the compounds contained the desired bicyclic framework, the double bond was at the $\Delta^{7,8}$ position rather than the desired $\Delta^{6,7}$ position (**Scheme 5.3**). After partial desilylation, the two products obtained were alcohol **5.6** and silyl ether **5.7**.



Scheme 5.3^a IMDA reaction with subsequent double bond migration.

^a Reagents: (i) $\text{BF}_3 \cdot \text{OEt}_2$ (1 equiv.), CH_2Cl_2 , 0 °C, 30 min, **5.6** (41%) and **5.7** (28%).

The ^1H and ^{13}C chemical shift data for **5.6**, along with the molecular connectivity information obtained from the HSQC and HMBC experiments are shown in **Figures 5.9** and **5.10**. A 2D NOESY experiment gave no useful information regarding the possible relative stereochemistry. A trace derived from a 1D TOCSY experiment that clearly shows the chemical shift and coupling of H6 (the upfield bridgehead hydrogen) is shown in **Figure 5.11**. This hydrogen (δ_{H} 1.85) was partially obscured by the vinyl methyl resonance (δ_{H} 1.87) in the ^1H nmr spectrum, making initial assignment of the spectroscopic data difficult.

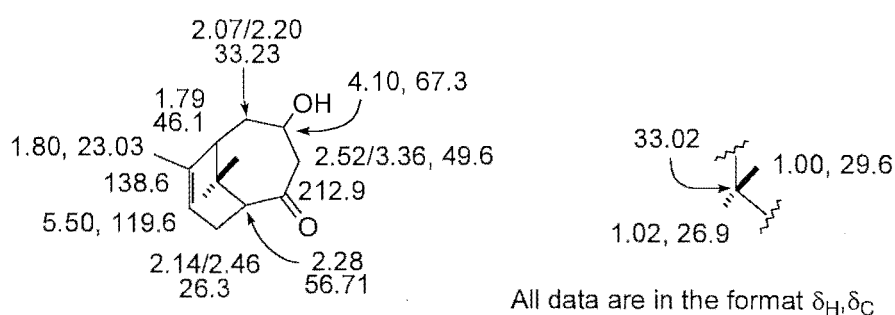


Figure 5.9 HSQC- and HMBC-based assignment of chemical shift data for **5.6**.

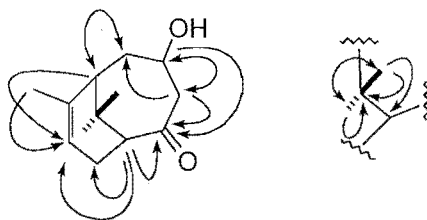


Figure 5.10 Key HMBC correlations for **5.6** that allowed connectivity to be assigned.

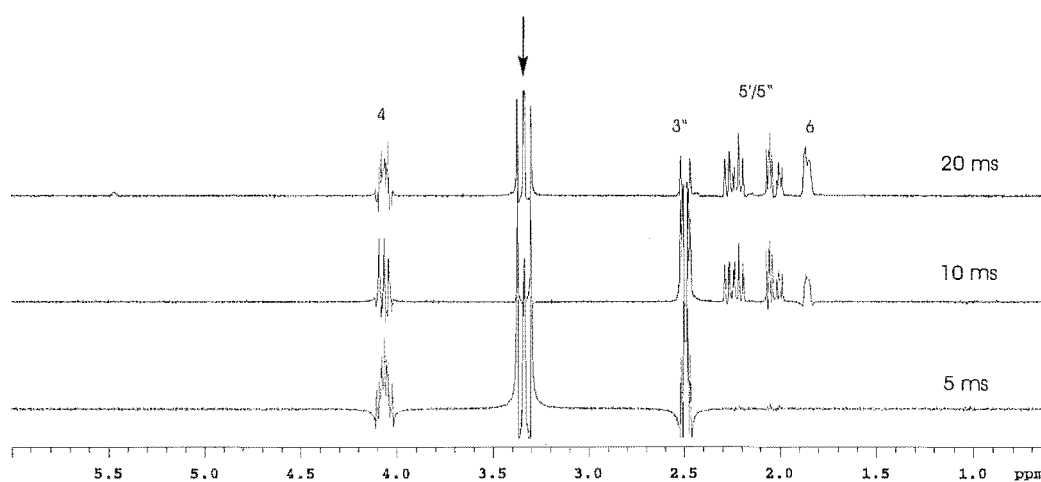


Figure 5.11 1D TOCSY from irradiation of the downfield H3 resonance (δ_{H} 3.35) of compound **5.6**. The irradiated resonance is arrowed.

Shea and Gilman have reported a related IMDA reaction in which no double bond isomerization was observed (**Figure 5.12**).¹³⁶

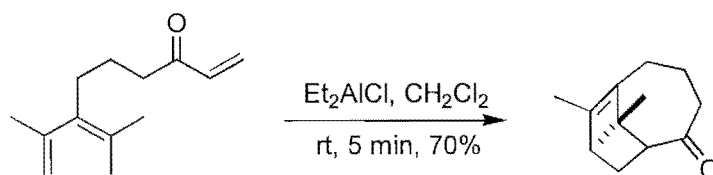


Figure 5.12 Shea's synthesis of bicyclo[4.3.1]decenes without isomerization.

A priori there are a number of possible mechanisms that would account for the observed migration.¹³⁷ However, under the reaction conditions, it is likely that only two possible

mechanisms may be operating: (1) a simple acid-catalyzed migration mechanism, or (2) a [1,3] sigmatropic shift (**Figure 5.13**).

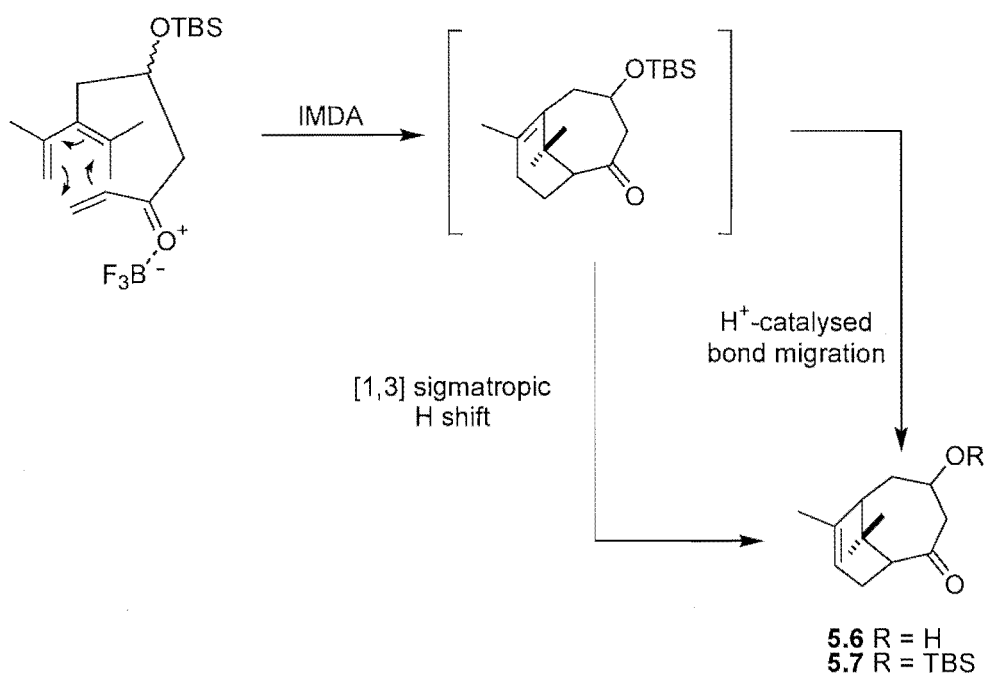


Figure 5.13 Possible mechanisms for the formation of adducts **5.6** and **5.7**.

Because of the antarafacial nature of [1,3]-hydrogen shifts, they are rare.¹³⁸ It seems reasonable to rule this possibility out on the basis of the further constraints enforced by the bicyclic system (**Figure 5.14**).

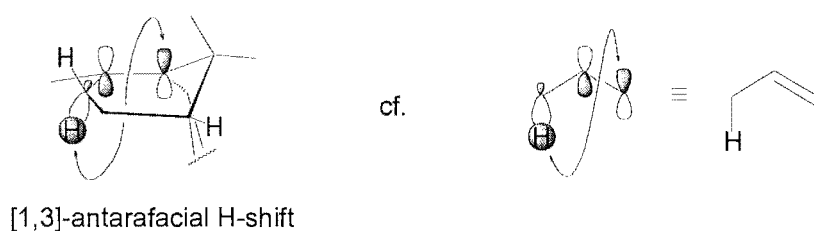
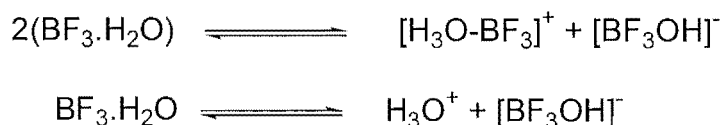


Figure 5.14 *LEFT:* The hypothetical [1,3]-antarafacial H-shift.
RIGHT: The prototypical [1,3]-antarafacial H-shift.

This leaves the acid-catalyzed process. Double bond migrations are known to be catalyzed by both protic and Lewis acids.¹³⁹ The thermodynamically most stable product is the one normally formed, and although the tetrasubstituted alkene would normally be expected to be the thermodynamically most stable alkene, there is probably some opportunity for the relief of strain by removal of the bridgehead double bond in this bicyclic system.¹⁴⁰ This would account for the observed product.

It is unclear whether the process is genuinely due to the Lewis acid or merely a consequence of the presence of adventitious water. In comparison to the other boron trihalides, boron trifluoride is relatively stable to hydrolysis.¹⁴¹ For example, it is known that boron trifluoride will react with water to give two hydrates, $\text{BF}_3 \cdot \text{H}_2\text{O}$ and $\text{BF}_3 \cdot 2\text{H}_2\text{O}$. Both hydrates partially dissociate into ions in the liquid phase, presumably as follows:



It is also known that when small amounts of boron trifluoride are passed into water, a solution of fluoroboric acid is obtained:



Any one of these mechanisms (or a combination of mechanisms) would allow the production of species that could result in double bond isomerization and/or hydrolysis of the silyl ether. A possible mechanism, based on this information, that proceeds *via* a protic acid is shown in **Figure 5.15**.

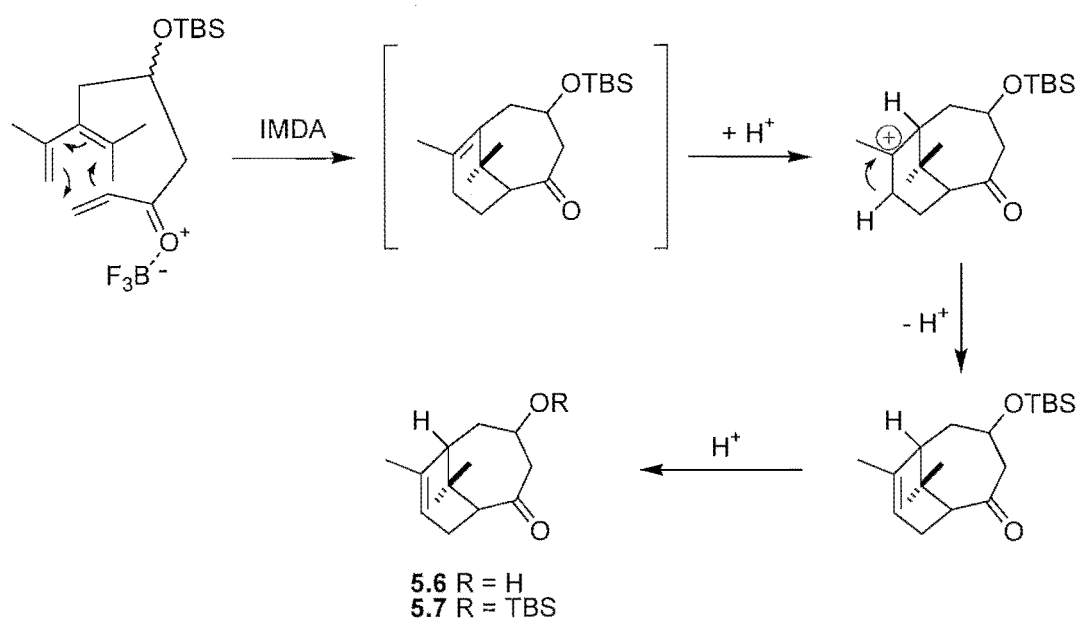


Figure 5.15 A possible mechanism for the formation of adducts **5.6** and **5.7**. It is possible that the order of the bond-migration and the desilylation could be reversed.

A protic acid catalyzed mechanism would also allow explanation of the results obtained by Shea and co-workers, who used an alkylaluminium Lewis acid. (**Figure 5.12**). The use of alkylaluminium halides as Lewis acids has been advocated as a method of ensuring anhydrous conditions.¹⁴² This recommendation is based on the dual nature of these aluminium species as both Lewis acids and Brønsted bases. To this end, it is possible that their use of diethylaluminium chloride both promotes the desired IMDA reaction, and also scavenges acid, thus not allowing the observed migration.

5.3.2 Stereochemistry of the Isomerized IMDA Adduct

It was expected that successful IMDA reactions would give compounds of stereochemistry as shown in **Figure 5.16**. This analysis is based on the expectation that the reaction would occur in an *endo* fashion *via* a chair conformation for the developing cycloheptane ring.¹⁴³ The silyloxy group is placed in the equatorial position on the developing cycloheptane ring. The corresponding twist-chair conformer could be expected to suffer from an unfavorable interaction between the silyloxy group and the

vinyl methyl group. This interaction may be significant in the transition structure for the cycloaddition, and would disfavor reaction *via* this conformer.

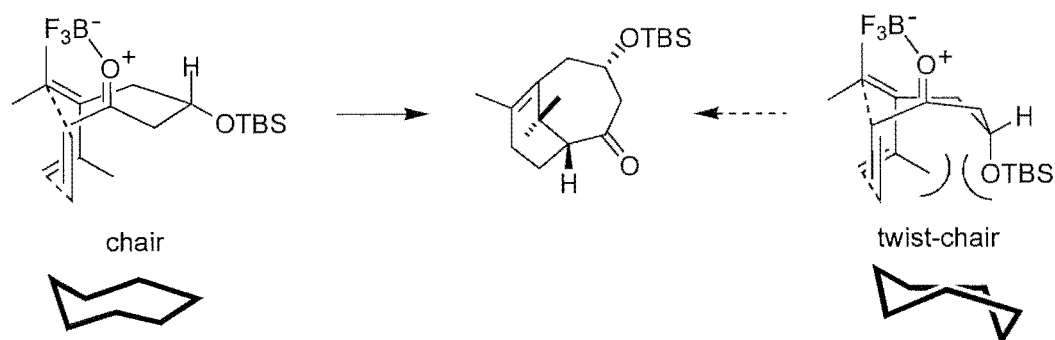


Figure 5.16 Stereochemistry prediction from the analysis of reactive conformers of **5.5**.

The conformers in which the stereochemistry is interchanged at the silyloxy group were also considered to be less likely due to transannular interactions between the silyloxy group and the ketone in the conformation required for reaction, or the proximal silyloxy and *gem*-dimethyl groups after cyclization (**Figure 5.17**).

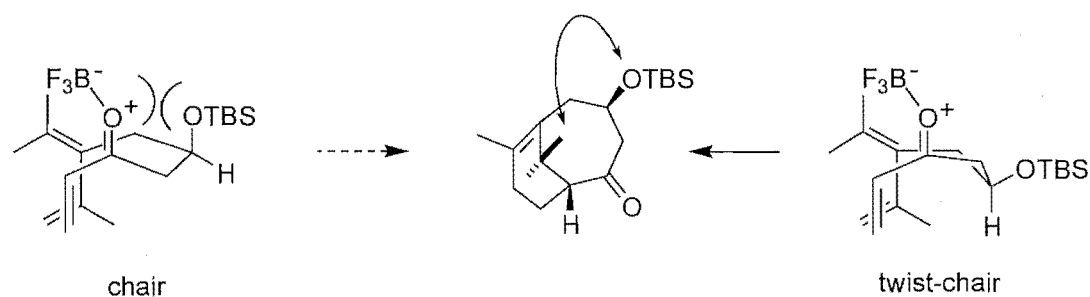
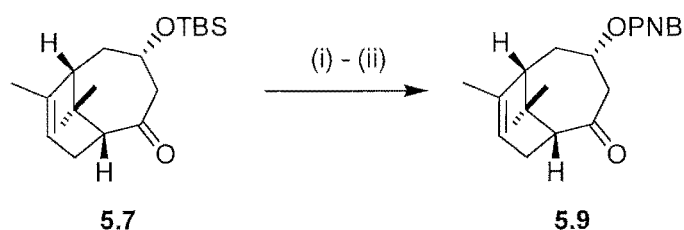


Figure 5.17 Conformers leading to the C4-epimeric IMDA adduct.

It was expected that the relative stereochemistry of the bridgehead hydrogens in compounds **5.6** and **5.7** would be *syn*, as the *anti* compound would almost certainly be too strained to be readily formed.

However, the lack of useful nOe data from compound **5.6** meant that it was necessary to explore alternatives in order to establish the stereochemical relationships in the molecule.

X-ray crystallography provided a straightforward solution to these questions. A crystalline derivative was synthesized as shown in **Scheme 5.4**. A sample of silyl ether **5.7** was desilylated with TBAF and the crude product (the previously isolated and characterized alcohol **5.6**) was acylated with 4-nitrobenzoyl chloride. This gave crystalline 4-nitrobenzoate **5.9** in 32% yield over two steps.



Scheme 5.4^a Preparation of a crystalline compound for X-ray analysis.

^a Reagents: (i) TBAF (5 equiv.), THF, 25 °C, 3 h; (ii) 4-nitrobenzoyl chloride, Et₃N, DMAP, CH₂Cl₂, 0 °C to 25 °C, 12 h, 32% for two steps.

Simple recrystallization of the product from 1:1 petroleum ether – ethyl acetate gave crystals suitable for X-ray analysis. A crystal was selected and the diffraction data collected. A diagram of the structure obtained after solution and refinement ($R_1 = 0.0435$, $wR_2 = 0.1016$) is shown in **Figure 5.18**.

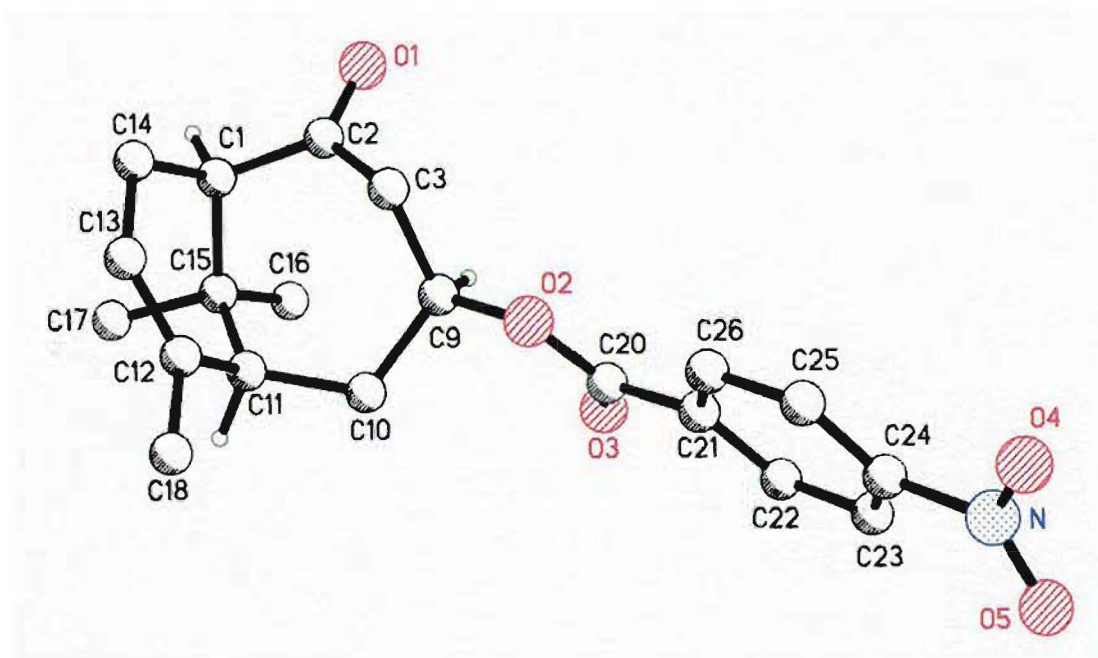


Figure 5.18 X-ray structure of 5.9. Atoms are of fixed, arbitrary radius.

This result is consistent with the IMDA reaction occurring *via* the conformer shown in **Figure 5.19** along with protonation from the face shown. This is consistent with the original reasoning outlined above.

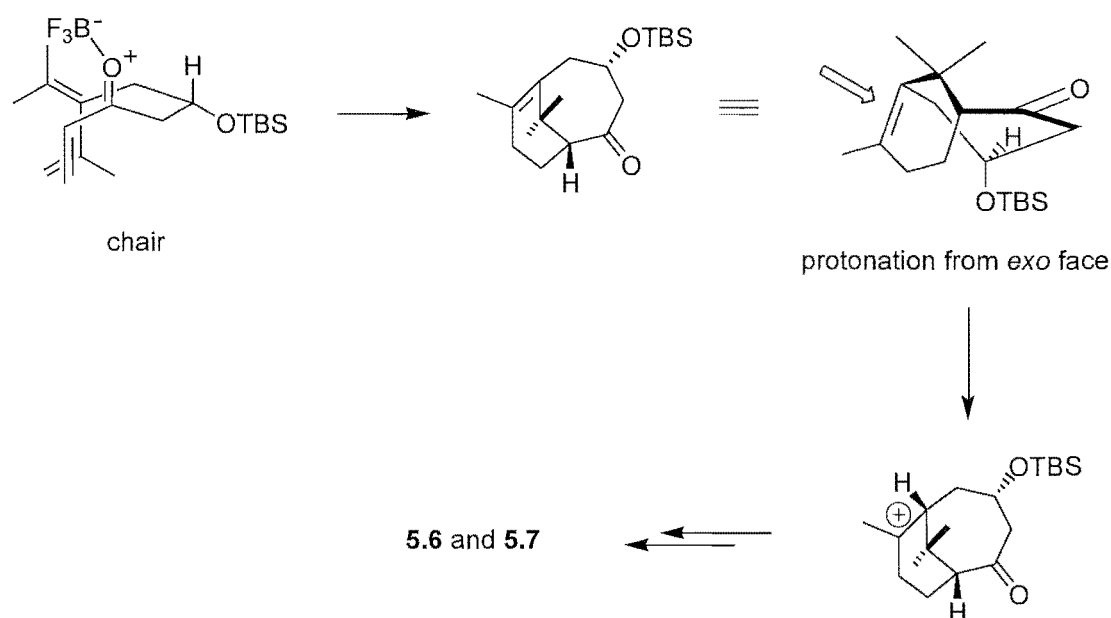


Figure 5.19 Models for the reactive conformation of **5.5** and face of protonation.

5.3.3 Efforts to Avoid Double-Bond Isomerization

Despite a number of research groups having reported taxane synthetic studies utilizing compounds with a $\Delta^{12,13}$ -alkene,⁵⁶ the isomerization of this bond into the desired $\Delta^{11,12}$ position in a bicyclic construct has not been reported to the best of the author's knowledge. Although it is possible to envisage methods for this transformation (see **Figure 5.20**), it would be simpler to avoid the isomerization in the first instance. Efforts to this end involved modifying the reagents and conditions as described below.

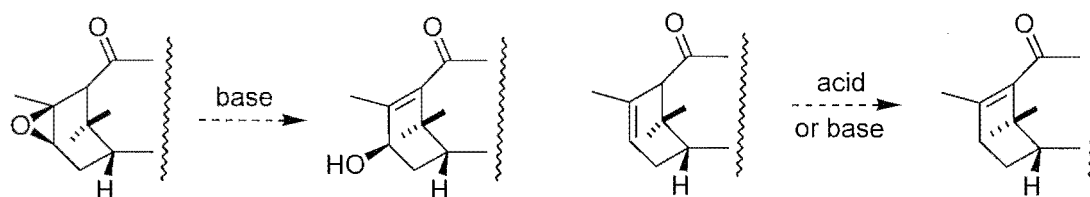


Figure 5.20 Possible methods for the introduction of the $\Delta^{11,12}$ -alkene (taxane numbering). Both are facilitated by a ketone at C10.

5.3.3.1 Redistillation of the $\text{BF}_3 \cdot \text{OEt}_2$

Given that the observations outlined above indicated that the boron trifluoride diethyl etherate may not be of sufficient purity or that adventitious water may be affecting the reaction, this avenue was investigated first. Although the boron trifluoride diethyl etherate originally used had been distilled from calcium hydride and stored under argon, it was redistilled again from calcium hydride immediately prior to use. The enone was also dried by repeated azeotropic evaporation to dryness with benzene before use. However, even with these precautions, the same isomerized adducts were isolated when the diene was exposed to one equivalent of boron trifluoride diethyl etherate for 30 minutes at 0°C in CH_2Cl_2 .

5.3.3.2 High-Pressure IMDA Reactions

Diels–Alder reactions under high-pressure have been used to perform reactions that are either slow or impossible under standard conditions.¹⁴⁴ The opportunity to explore this avenue was raised by Professor Lew Mander.[†]

The rate of reaction can be written as a function of the activation volume ΔV^\ddagger :

$$\frac{\delta \ln k}{\delta p} = \frac{\Delta V^\ddagger}{RT}$$

The activation volume is the difference in molar volume (strictly speaking in partial molar volume) between the activated complex and the reactants from which it was derived.

If the transition state volume is smaller than the starting materials (ie ΔV^\ddagger is negative) then pressure will accelerate the reaction. However, when ΔV^\ddagger is positive, the reaction

[†] The author would like to thank Professor Lew Mander and Mr Tim O’Sullivan, both of the Australian National University, Canberra, Australia for performing these reactions.

rate will be decreased by increased pressure. The variation of rate as a function of pressure for a reaction with a ΔV^\ddagger of $-20 \text{ cm}^3 \text{ mol}^{-1}$ is shown in **Figure 5.21**.¹⁴⁴

Intramolecular Diels-Alder reactions are known to have large negative volumes of activation (measured values¹⁴⁵ range from *ca* $-25 \text{ cm}^3 \text{ mol}^{-1}$ to $-35 \text{ cm}^3 \text{ mol}^{-1}$). As a consequence of this, the application of pressure can be expected to have a significant effect on the rate of reaction. Despite this, examples of IMDA reactions at high pressure are relatively uncommon compared to their intermolecular counterparts.¹⁴⁵

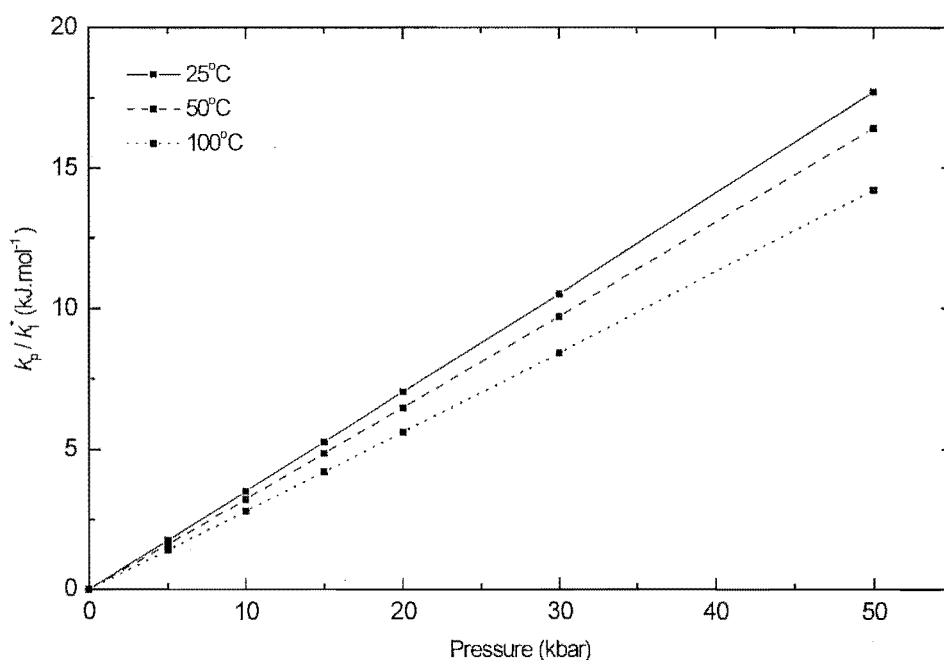


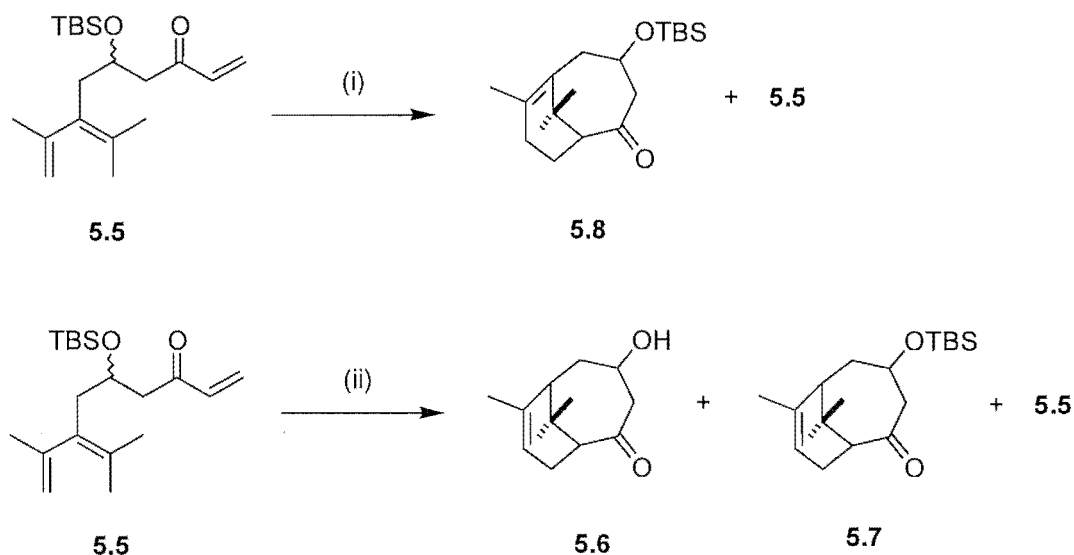
Figure 5.21 Rates of IMDA reactions at pressure. The data is taken from ref 144. k_p = the rate at the indicated pressure; k_i^* = the rate at 1kbar. The y-axis is in the \log_{10} of k_p/k_i^* . It should be noted that at pressures greater than 10 kbar, the system does not strictly obey the ideal rate equation as ΔV^\ddagger is pressure dependent. Nonetheless, ΔV^\ddagger generally decreases with increased pressure.

With respect to the reaction at hand it was hoped that the use of high-pressure might alter the product distribution. If the isomerization reaction proceeds *via* a protonation mechanism, then ΔV^\ddagger for this reaction would probably be less negative than the IMDA, or possibly even positive. Because of this, the use of increased pressure could be expected to retard the rate of isomerization.

In the initial experiment, diene **5.5** was dissolved in the minimum volume of CH_2Cl_2 , and the solution was pressurized at 25 °C and 19 kbar for 24 hours. After removal of the solvent, the crude reaction mixture was analyzed by ^1H nmr. The spectrum of the crude product showed starting material and a new compound in a ratio of approximately 1 to 4. Resonances at δ_{H} 1.02 and δ_{H} 1.08 were tentatively assigned to the *gem*-dimethyl group of a cycloadduct. Significantly, there was no resonance corresponding to the trisubstituted alkene at *ca* δ_{H} 5.5). Subsequent comparison of this spectrum with the spectroscopic data obtained for compound **5.8** (*vide infra*) confirmed the presence of the desired compound.

A further sample of the diene was dissolved in the minimum of CH_2Cl_2 and pressurized at 55 °C and 16 kbar for 64 hours. Upon cooling to room temperature and removal of the solvent, the reaction was analyzed by ^1H nmr. This analysis indicated the presence of starting material and two cycloadducts in a 1:2:2 ratio. However, it was clear from the spectroscopic data that the cycloadducts were the previously isolated alcohol **5.6** and silyl ether **5.7**.

These results are summarized in **Scheme 5.5**. However, this avenue was not pursued further due to the concurrent discovery of Lewis acid catalyzed conditions for the cycloaddition (*vide infra*).



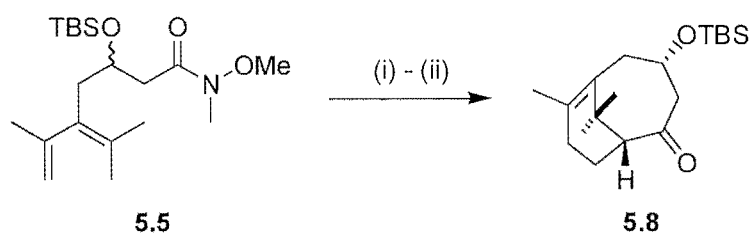
Scheme 5.5^a High-pressure Diels-Alder reactions.

^a Conditions: (i) CH₂Cl₂, 25 °C, 19 kbar, 24 h, 4:1 **5.8**:**5.5** (by ¹H nmr); (ii) CH₂Cl₂, 55 °C, 16 kbar, 64 h, 2:2::1 **5.6**:**5.7**:**5.5** (by ¹H nmr).

5.3.4 The IMDA without Isomerization

The discovery of conditions for the IMDA reaction without concomitant double-bond isomerization was somewhat serendipitous. Initial studies had indicated that boron trifluoride diethyl etherate at -78 °C did not catalyze the reaction (as described above in **Section 5.3.1**). However, as part of a subsequent investigation, diene **5.5** was treated with a large excess of boron trifluoride diethyl etherate (10 equivalents) in CH₂Cl₂ at -78 °C. These conditions resulted in clean transformation of starting material into a single new compound (within one hour as judged by TLC analysis). Standard aqueous workup and analysis of the crude reaction mixture by ¹H nmr showed the presence of a cycloadduct. Examination of the spectrum showed singlets at δ_{H} 1.02 and δ_{H} 1.09. These resonances were assigned to the *gem*-dimethyl group of the cycloadduct. There were no resonances in the δ_{H} 5.00 – 6.00 region. The spectroscopic data was consistent with the desired cycloadduct, without double-bond isomerization (**Scheme 5.6**). This sequence was performed without purification of the intermediate enone, as earlier

studies had indicated that purification of the enone resulted in significant loss of material, with only slight gains in purity.



Scheme 5.6^a IMDA reaction *without* subsequent double bond migration.

^a Reagents: (i) vinylmagnesium bromide (2.5 equiv.), THF, reflux, 1 h; (ii) BF₃·OEt₂ (10 equiv.), CH₂Cl₂, -78 °C, 1 h, (43% for two steps).

After purification of the crude IMDA reaction mixture by flash chromatography, the compound was subjected to a full range of two-dimensional nmr experiments. These experiments confirmed the identity of the compound obtained as **5.8**. The ¹H and ¹³C chemical shift data for **5.8**, along with the connectivity information obtained from the HSQC and HMBC experiments are shown in **Figures 5.23** and **5.24**. Due to a substantial amount of overlap of the methylene resonances, it was not until the HMBC data from an experiment set up to select for various values of the long-range coupling constant ⁿJ_{CH}, were obtained that a definitive assignment could be made. The only notable correlation in the 2D NOESY spectrum was from the upfield *gem* methyl signal (δ_H 1.02) to the CHOTBS proton (δ_H 4.15).

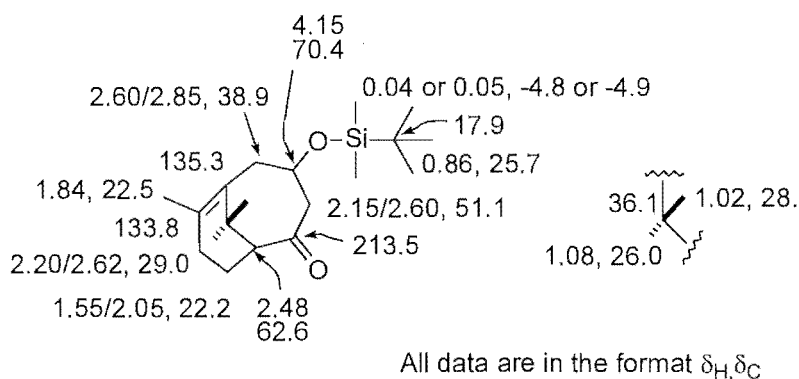


Figure 5.23 Chemical shift data for **5.8**.

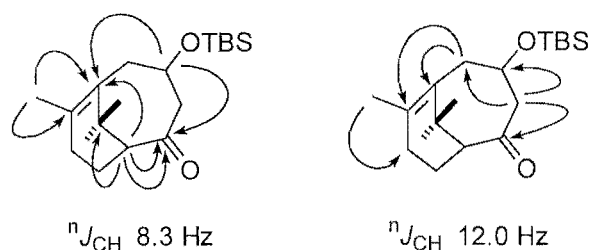
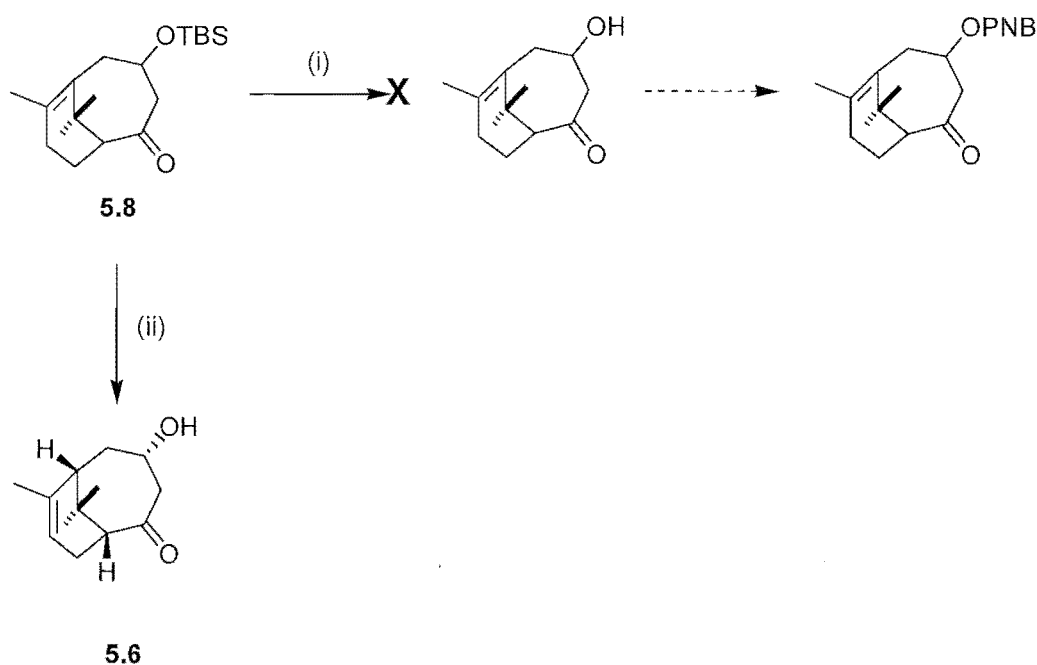


Figure 5.24 Connectivity data obtained from HMBC experiments on **5.8**. The non-ambiguous correlations are shown for ${}^nJ_{\text{CH}} = 8.3 \text{ Hz}$ and the correlations that allowed assignment of the methylene signals are shown for ${}^nJ_{\text{CH}} = 12.0 \text{ Hz}$.

5.3.5 Stereochemistry of the IMDA Adduct

Based on the arguments outlined in **Section 5.3.2**, it was expected that the stereochemistry of the IMDA product **5.8** was as shown in **Scheme 5.5**. Despite having conclusive proof of stereochemistry for the isomerized compound **5.9** from a single crystal X-ray analysis, further proof of stereochemistry for **5.8** was sought. An attempt to desilylate this compound under basic conditions with TBAF (as shown in **Scheme 5.7**) was unsuccessful. The ${}^1\text{H}$ nmr spectrum of the crude reaction mixture indicated a number of compounds, including an aldehyde. This result is readily rationalized through a retro-aldol reaction occurring under these conditions. However, this thwarted efforts to produce a crystalline compound for X-ray analysis as it was not possible to introduce a group that would aid crystallinity.



Scheme 5.7^a Transformations of IMDA adduct **5.8**: stereochemistry by correlation to a known compound.

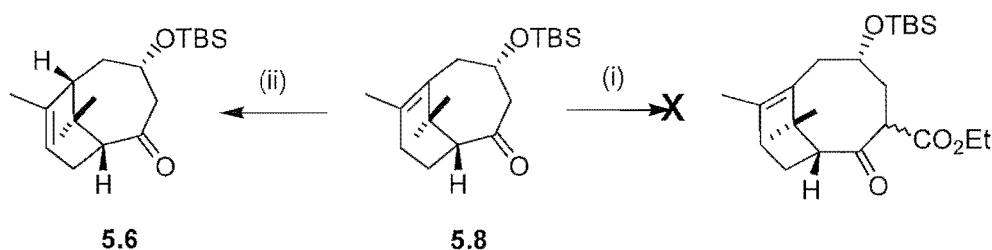
^a Reagents: (i) TBAF (5 equiv.), THF, 25 °C, 3 h; (ii) BF₃·OEt₂ (2 equiv.), CH₂Cl₂, 0 °C to 25 °C, 1 h.

The proof of stereochemistry for compound **5.8** rests upon the second transformation shown in **Scheme 5.7**. Treatment of **5.8** with boron trifluoride diethyl etherate (2 equivalents) in CH₂Cl₂ from 0 °C to 25 °C over a period of one hour resulted in two compounds by TLC. ¹H NMR analysis showed these two compounds to be present in a ratio of *ca* 2.5:1. The minor compound was the alcohol **5.6**, which has been previously characterized. The major compound was not characterized. It is unlikely that the isomerization reaction would result in alteration of the stereochemistry, so it follows that the stereochemistry proposed for **5.6** is also that of **5.8**. This is also consistent with the analysis of likely reactive conformations of the IMDA adduct discussed earlier (**Section 5.3.2**).

5.4 Preliminary Ring-Expansion Studies

The availability of **5.8** made it possible to briefly investigate the ring-expansion of this compound. Time constraints meant that it was possible to investigate only two methods.

Treatment of the IMDA adduct with ethyl diazoacetate (one to five equivalents) in the presence of boron trifluoride diethyl etherate at various temperatures failed to result in ring-expansion (**Scheme 5.8**).¹⁴⁶ Starting material was recovered from these reactions. The use of antimony chloride at -78°C was more promising, resulting in the formation of a new compound by TLC. However, analysis of the ¹H nmr spectrum of the crude product of the reaction after quenching indicated that the major compound present was **5.6** (see also **Scheme 5.8**).

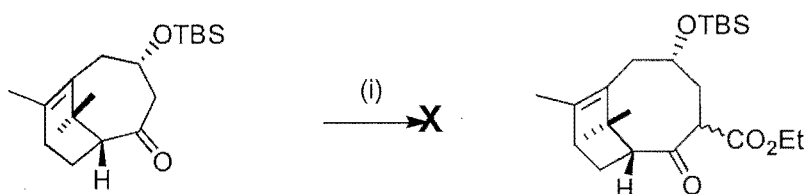


Scheme 5.8^a Preliminary efforts to ring-expand **5.8** by *via* ethyl diazoacetate mediated ring expansion

^a Reagents: (i) ethyl diazoacetate, BF₃·OEt₂, 0 °C to 25 °C, 1 h, OR - 78 °C, 1 h; (ii) ethyl diazoacetate, SbCl₅, 2 h.

An alternative anionic method was also explored in an effort to overcome the lack of success with the Lewis acid facilitated addition of the ethyl diazoacetate to the ketone.¹⁴⁷ Ethyl lithiodiazoacetate was generated from ethyldiazoacetate with lithium hexamethyldisilazide, lithium diisopropylamide, or *n*-butyllithium. Addition of a solution of **5.8** to the ethyl lithiodiazoacetate solution resulted in a pale orange-yellow

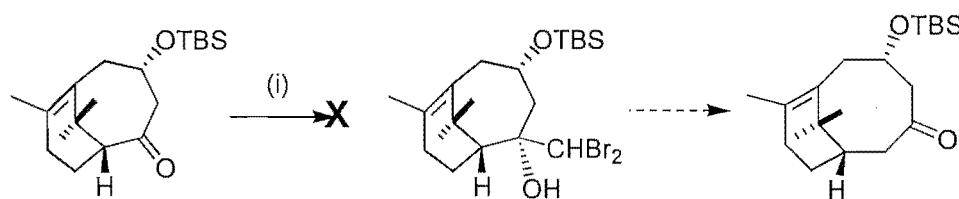
solution. Quenching these reactions resulted in the recovery of starting material (**Scheme 5.9**). Similar observations and results were noted upon trying to generate ethyl lithiodiazoacetate in the presence of the ketone. Although not investigated further, these observations may be indicative of facile enolization of **5.8** rather than the desired addition to the ketone.



Scheme 5.9^a Attempted ring-expansion using ethyl lithiodiazoacetate.

^a Reagents: (i) ethyl lithiodiazoacetate (generated by several methods), THF, -78 °C, 30 min.

An alternative strategy based around the addition of dibromomethyl lithium to the ketone of **5.8**, followed by carbene formation from the adduct and subsequent ring-expansion was also briefly explored.¹⁴⁸ However, the addition of bromomethyl lithium to **4.8** gave complicated product mixtures. Inspection of the ¹H nmr spectra of these reactions did not indicate the presence of the desired product (**Scheme 5.10**).



Scheme 5.10^a Attempted ring-expansion *via* dibromomethyl lithium addition and carbene formation.

^a Reagents: (i) LiCHBr₂, Et₂O-THF, -95 °C to -78 °C, 30 min.

The difficulties in adding nucleophiles to the ketone of **4.8** indicate that investigation of the cyclopropane cleavage strategy outlined in **Figure 5.6** may be worthwhile.

However, it is also possible that other anionic methods may yield fruitful results, and these methods can not be ruled out without further investigation.

5.5 Summary

The intramolecular Diels–Alder synthesis of bicyclo[4.3.1]decene system **5.8** has been described.

The optimal conditions for the IMDA reaction involve the use of excess boron trifluoride diethyl etherate at -78 °C. Higher temperatures result in isomerization of the double bond and partial desilylation to give compounds **5.6** and **5.7**.

A brief investigation also indicated that the use of high-pressure at room temperature may provide a viable route to **5.8**.

A possible explanation for the isomerization of the double bond has been provided.

Preliminary studies have indicated that the ring-expansion *via* addition of nucleophilic species may be difficult. Observations made during these experiments indicate that enol silylation, cyclopropanation, and ring-expansion by cyclopropane cleavage may be a more promising approach.

Chapter Six

Summary and Future Potential of these Studies

Although progress towards the ultimate goal of this research—a total synthesis of taxinine—has been modest, this work has addressed a number of issues. The information gained from this research allows some conclusions to be reached and also allows for refinements to the original strategy to be made.

It has been established that the ring-closing metathesis of the acyclic diene shown in **Figure 6.1** to give a bicyclic system is not feasible. Whilst discouraging, several aspects of this strategy are worthy of further comment. Firstly, it is possible that the stereochemistry of the C2 substituent is significant. Although it was not investigated in this thesis, a synthesis of the epimeric alcohol should be possible based on the procedure that was developed to invert the stereochemistry at this position (**Figure 6.2**).

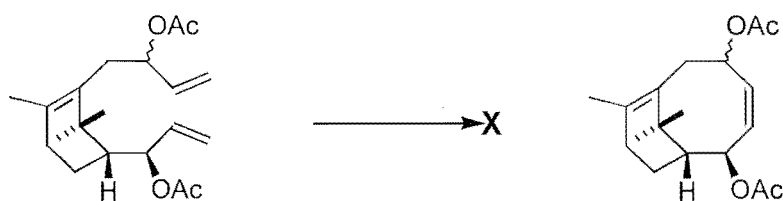


Figure 6.1 The failed RCM ring closure.

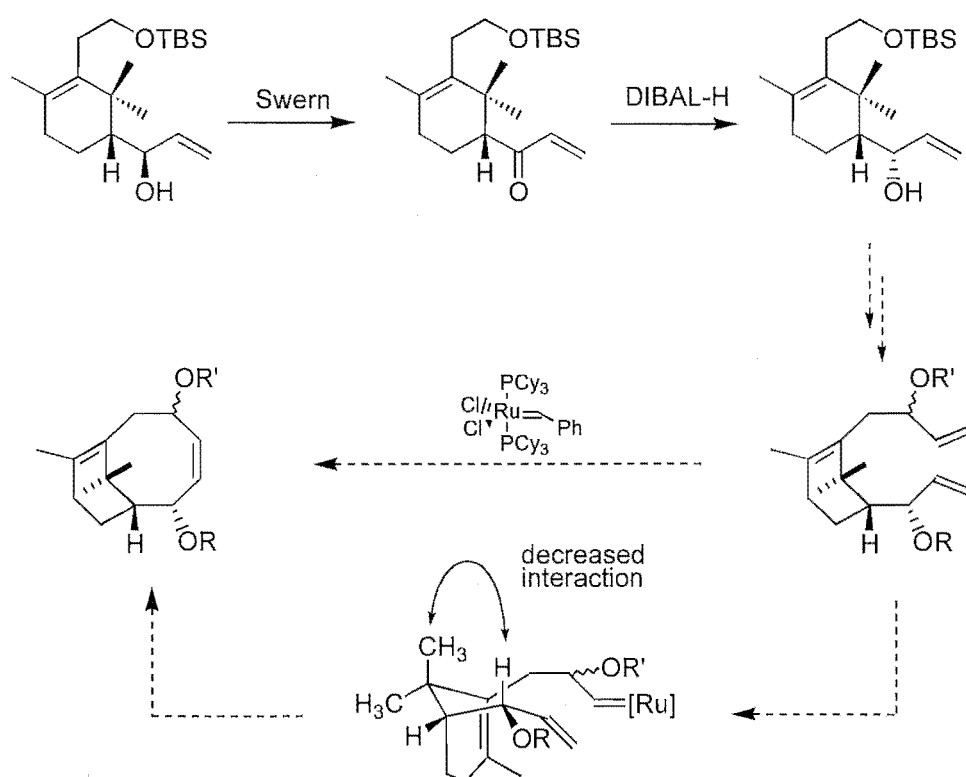


Figure 6.2 A proposed route to the epimeric RCM substrate based on the inversion of the Grignard adduct. The inversion of the stereochemistry could be expected to decrease the interaction between the C2 substituent and the *gem*-dimethyl group.

It may also be possible to entirely remove the C2 substituent, although this would probably preclude access to C2-oxygenation taxanes such as taxinine. Nonetheless, if ring-closure on a C2-deoxygenated construct can be achieved, then this strategy should be applicable to taxanes such as taxusin (**Figure 6.3**).

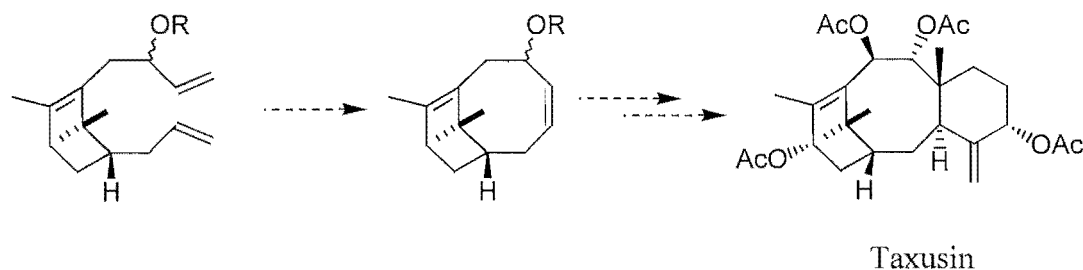


Figure 6.3 RCM of C2-deoxygenated constructs. Potential for taxusin synthesis.

The issues surrounding the stereochemistry and functionality at C2 clearly warrant further attention as it would allow firmer conclusions to be drawn on the viability of a RCM closure at this position. This is reinforced by the recent synthesis of a bicyclic taxane system by RCM by Blechert and co-workers (**Figure 6.4**).¹⁴⁹ The success of this ring-closure may depend on the use of a system without a bridgehead double bond. The stereochemistry at C11 should also allow the dienes to be brought sufficiently close for RCM to occur without significant interactions with the *gem*-dimethyl group. However, as commented upon earlier (**Section 5.3.3**), the isomerization of the double bond to the correct $\Delta^{11,12}$ position has yet to be demonstrated (to the best of the author's knowledge).

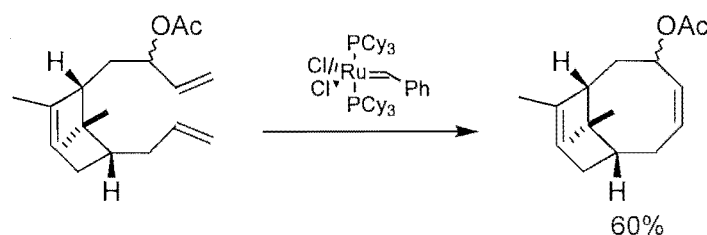


Figure 6.4 Blechert's synthesis of a taxane AB-ring system by RCM.

In the context of a total synthesis, it is the author's opinion that the inversion or removal of the C2 substituent would substantially detract from the elegance of the route.[†] For this reason, the intramolecular Diels-Alder (IMDA) route investigated in **Chapter 5** is more worthy of further attention. The results in this thesis have clearly demonstrated that a suitably substituted bicyclo[4.3.1]decane system can be prepared by Lewis acid catalyzed IMDA reaction. There is also some potential for the investigation of high-pressure as a method for the construction of bridgehead cycloalkenes. Further investigation should hopefully yield a suitable ring-expansion protocol for the bicyclo[4.3.1]decane system.

The potential use of ring-closing metathesis for the annelation of the taxane C-ring has been demonstrated in **Chapter 4**. The model study has shown that this method should provide a concise way to add the C-ring to appropriately functionalized systems. Because of the constraints imposed by fusion to a five-membered ring, there were some difficulties encountered in the model study. These difficulties are not expected to be as prevalent in a taxane setting as the formation of the *trans*-fused BC-ring junction where one of the rings is eight-membered should be more facile. Recent results from Grubbs' laboratories have shown that ruthenium carbenes can catalyze the formation of

[†] A similar viewpoint has been eloquently voiced by Clayton Heathcock:

"There definitely **are** kinds of total syntheses activities that people should avoid. One of our problems is that many practitioners don't exercise sufficient judgement about whether a synthesis represents an improvement over prior art. It damages our collective image when someone publishes a total synthesis of a compound that has been synthesized several times before, and the new synthesis is twice as long and uses steps that proceed in poorer yield. This kind of total synthesis does not represent an advance, but is really a step backwards.

These inferior syntheses are not usually created on purpose, but begin with a good idea that just doesn't work out. The chemist then does whatever possible to complete the synthesis, usually involving a much longer and more cumbersome route than was originally envisioned...."

Heathcock, C. H. *As We Head Into The 21st Century, Is There Still Value In Total Synthesis Of Natural Products As A Research Endeavor?*. In *Chemical Synthesis: Gnosis to Prognosis*. Chatgililoglu, C. and Snieckus, V. Kluwer: Dordrecht, 1996.

trisubstituted double bonds.¹⁵⁰ This should allow for the direct introduction of the C20 carbon by the RCM strategy demonstrated here.

The results obtained in **Chapter 4** have also indicated that there is potential for the use of RCM as a general method for the annelation of rings to form fused carbocycles (**Figure 6.5**). This area is deserving of further research.

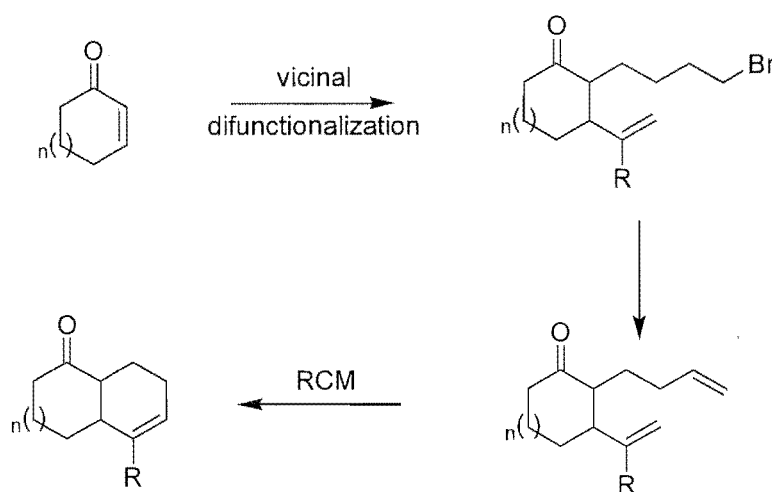


Figure 6.5 Potential for the formation of fused carbocycles. A number of positions for ring-closures are possible, and only one is shown.

Clearly, a major obstacle to a synthesis of taxinine by this strategy is the lack of a viable route to a bicyclic enone. If it is possible to secure a route to the desired enone system, then a synthesis of taxinine should be possible following the work delineated in this thesis and work already in the literature. An overview of these ideas is provided in **Figure 6.6** (see over page).

Should research to this end prove fruitless, then an alternative strategy is available for taxane synthesis from the dithiane compounds prepared in **Chapter 4**. Shea, Jenkins and others have demonstrated the ability of the IMDA reaction to form the taxane skeleton and also bicyclo[4.4.1]undecanes. However, a major problem has been the

synthesis of suitable C-ring building blocks from which to begin this approach. Dithianes of the general type shown in **Figure 6.7** (see over page) should prove useful as building blocks from which to explore this alternative, and it may also prove possible to conduct the IMDA reaction on acyclic systems as shown in **Figure 6.8** (see over page).

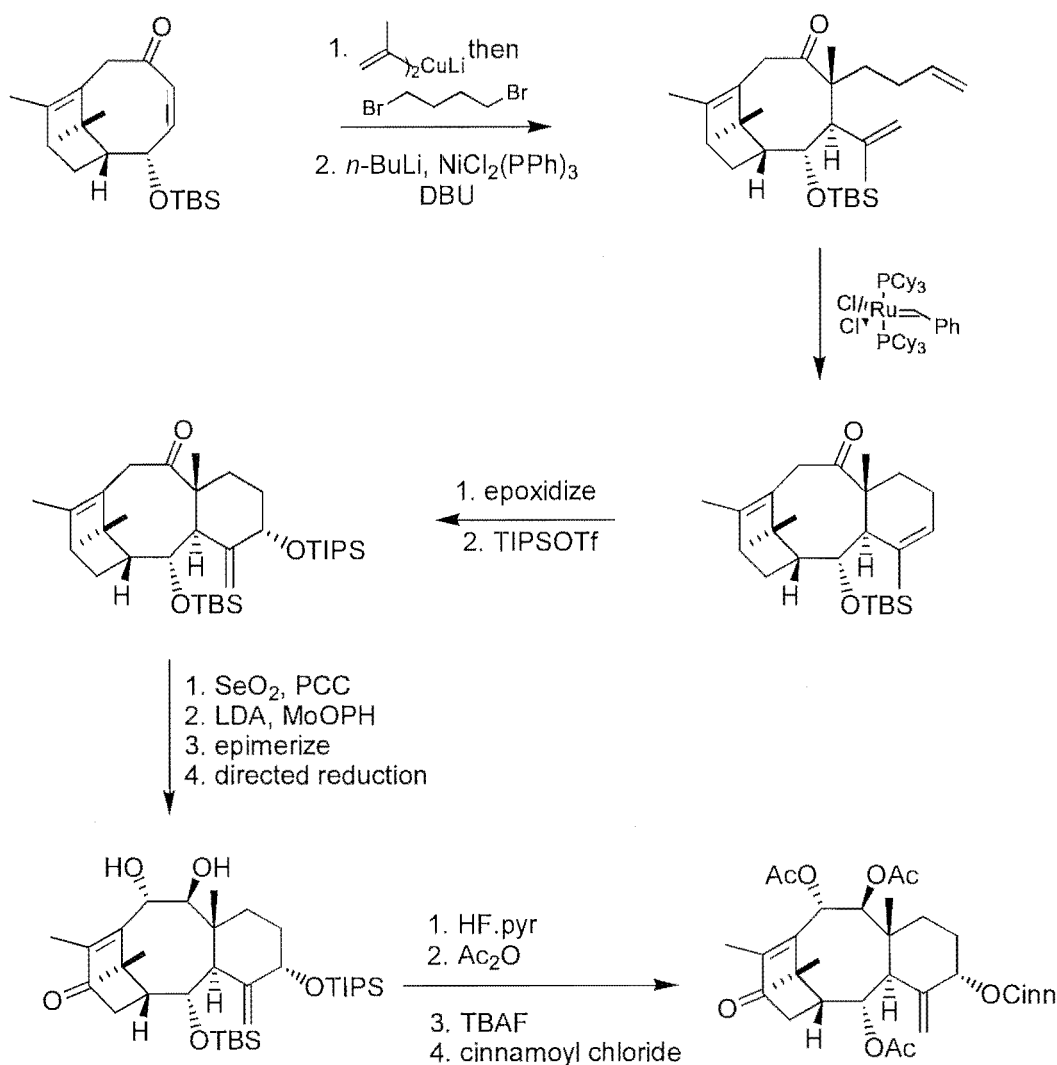


Figure 6.6 The proposed completion of a taxinine synthesis. Some questions remain regarding protocols for enolate hydroxylation and the possible need for epimerization, although these transformations have been demonstrated in related systems.

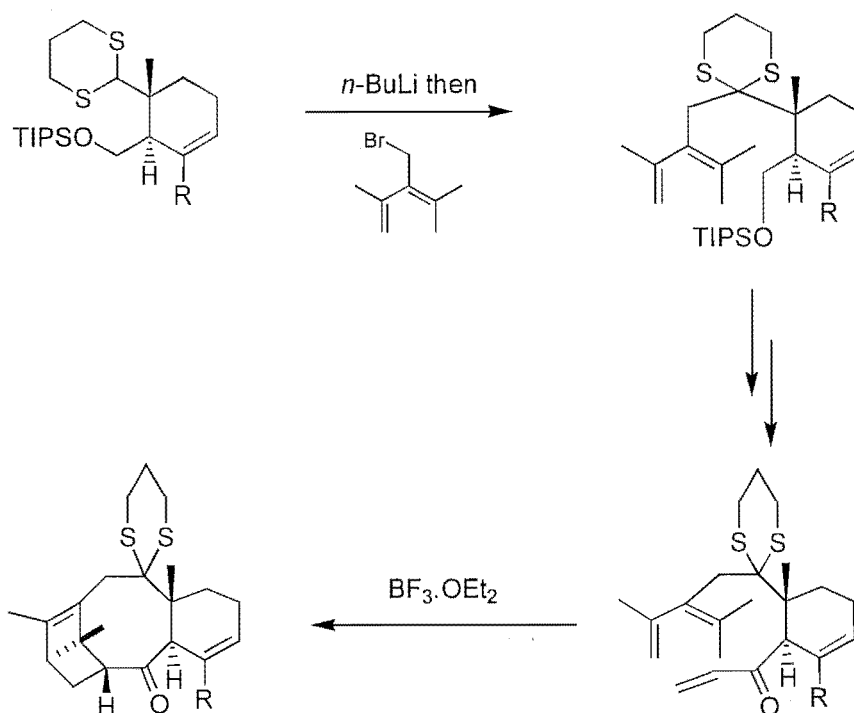


Figure 6.7 Potential uses for RCM-derived dithianes as the starting point for C→ABC IMDA strategies.

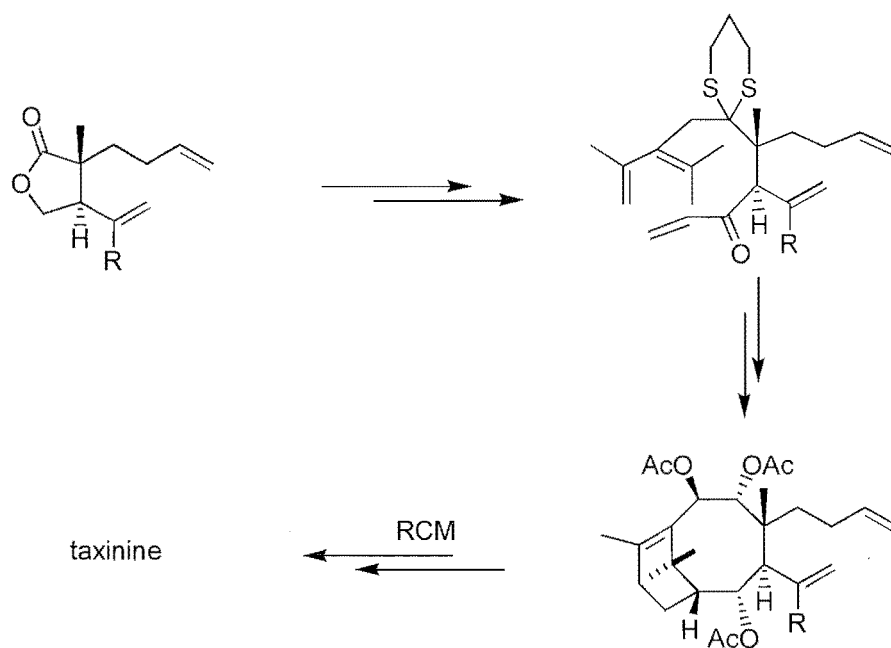


Figure 6.8 The possibility of IMDA prior to RCM closure of a C-ring.

Whilst a substantial amount of work remains before a synthesis could be completed, the studies in this thesis have allowed some progress towards the development of a new strategy for taxane synthesis, and also have provided some useful building blocks that may be employed in existing strategies.

Chapter Seven

Experimental

7.1 General Methods

7.1.1 Nuclear Magnetic Resonance

Proton detected NMR spectra were obtained on either a Varian Unity 300 spectrometer or a Varian XL300 spectrometer, both operating at 300 MHz. Carbon detected NMR spectra were obtained on the XL300 spectrometer operating at 75 MHz. Unless otherwise indicated spectra were obtained at 23 °C. The other NMR experiments described in this thesis viz. 1D-TOCSY, 2D-TOCSY, COSY, NOE, NOESY and the reverse-detected HSMQC, HSQC and HMBC experiments were all obtained on the Unity 300 spectrometer at 300 MHz. At various stages this instrument was fitted with either a Nalorac Z.spec MID300 3 mm Indirect Detection Probe or a Pulsed Field Gradient MLD driver with a 5mm Indirect Detection Probe. Chemical shifts in this thesis are described in parts per million (ppm), on the δ scale, and are referenced to the appropriate solvent peaks: CDCl_3 referenced to CHCl_3 at δ_{H} 7.26 and CHCl_3 at δ_{C} 77.01; CD_2Cl_2 referenced to CHDCl_2 at δ_{H} 5.33; DMSO-d_6 referenced to $(\text{CD}_3)(\text{CHD}_2)\text{SO}$ δ_{H} 2.50 and $(\text{CD}_3)_2\text{SO}$ δ_{C} 39.60. ^1H NMR spectra were obtained using an acquisition time (A_t) of 2 s. ^{13}C NMR spectra were obtained with an A_t of 0.878 s and typically a delay (D_1) of 1 s. The usual ^{13}C spectroscopic parameters of 17094 Hz (227.92 ppm) window and 30016 data points give a digital resolution of 0.57

Hz per data point (0.008 ppm per data point). Thus ^{13}C data in this thesis are reported to two decimal places. APT experiments were obtained using an A_t of 0.878 s. All difference NOE experiments were obtained in undegassed solutions, with an acquisition time (A_t) of 1 s and an irradiation time (D_2) of 2 s. The decoupler was offset 10,000 Hz for the control experiment. Percentage enhancements reported in this thesis represent the observed increase in the intensity of a specific resonance relative to the corresponding signal in the control spectrum. NOESY experiments were run using an A_t of 0.468 s and a mixing time of 0.30 s. With the pulse field gradient system 1D-NOESY experiments were run with an A_t of 1.0 s, and D_2 of 2.0 s. COSY experiments were obtained using an acquisition time of 0.216 s and a relaxation delay of 1 s. 1D-TOCSY spectra were obtained using an A_t of 2.0 s, a D_1 of 1.0 s and mixing times as indicated in the discussion. HSMQC experiments were obtained with an A_t of 0.2 s, D_1 was set for individual samples when setting the null value and $^1J_{\text{CH}} = 145$ Hz. HSMQC-TOCSY experiments were run with the same parameters as the HSMQC with the addition of a mixing time array of 0.02 and 0.08 s. HMQC experiments with the pulsed field gradient system were run with an A_t of 0.137 s, a D_1 of 1.0 s and $^1J_{\text{CH}} = 140$ Hz. HMBC experiments were obtained with an A_t of 0.21 s (0.137 s with the pulsed field gradient system), a relaxation delay of 0.3 s, $^1J_{\text{CH}} = 140$ Hz and $^nJ_{\text{CH}} = 8.3$ Hz, unless otherwise stated.

7.1.2 Mass Spectrometry

Mass Spectrometry was performed on a Kratos MS80 Mass Spectrometer operating at 4 kV. Various ionization techniques were used including Electron Impact (EI) at 70eV and chemical ionization (CI; C_4H_{10}). Fast Atom Bombardment (FAB) was used where necessary and was performed with an Ion Tech ZN11FN ion gun using Xe as the reagent gas, operating at 8 kV and 2 mA with either NOBA (m-nitrobenzyl alcohol), m-b (magic bullet, 50% dithioerythritol/dithiothreitol), or glycerol as the matrix. GCMS

conditions were: DB5 column 30m x 0.25mm x 0.25 μ m (thickness of film), oven 50(1) - 260(15) °C ramped at 10 degrees/min, scan 500-30 @ 0.25 s/decade, calibration 430-44, Library: Wiley NBS for matching.

7.1.3 IR Spectroscopy

IR spectra were obtained using a Shimadzu 8201PC Series FTIR interfaced to a Intel 486 PC running Shimadzu's HyperIR software. Spectra were run neat on either a KBr or CaF₂ disc, or in a solution of CDCl₃.

7.1.4 Reagents and Solvents

Unless otherwise indicated, all reactions were conducted in oven- or flame-dried glassware under an atmosphere of dry nitrogen or argon. Analytical thin layer chromatography (TLC) was conducted on aluminium- or plastic-backed Merck Kieselgel KG60F₂₅₄ silica plates. Visualization was by short-wave ultraviolet light and/or staining with vanillin or potassium permanganate solutions. Flash chromatography was performed on Merck Silica 60 following the guidelines given by Still and coworkers.¹⁵¹ Solvents and reagents used in reactions were purified according to well-established procedures.¹⁵² Tetrahydrofuran (THF), diethyl ether and benzene (PhH) were distilled from sodium benzophenone ketyl immediately prior to use. Benzene used for metathesis reactions was distilled from calcium hydride immediately prior to use. Toluene was distilled from phosphorus pentoxide and stored over sodium wire. Dimethyl sulphoxide (DMSO), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone (DMPU) and hexamethylphosphoric triamide (HMPA) were all distilled under reduced pressure from calcium hydride and was stored under N₂ or Ar over 4Å molecular sieves. *N,N*-Dimethylformamide (DMF) was dried by standing over freshly

activated 4Å molecular sieves for two periods of 24 hours before finally being stored under N₂ or Ar over 4Å molecular sieves.¹⁵³ Dichloromethane (CH₂Cl₂), trimethylsilyl chloride (TMSCl), triethylamine (Et₃N), boron trifluoride diethyl etherate (BF₃.OEt₂), and Hünig's Base (*N,N*-diisopropyl-*N*-ethylamine) were all distilled from calcium hydride. *N,N,N,N*-Tetramethylethylenediamine (TMEDA) was distilled under N₂ from KOH pellets. Methanol (MeOH) and ethanol (EtOH) were distilled from iodine-magnesium turnings and stored under N₂ or Ar over 4Å molecular sieves. Lithium diisopropylamide (LDA), lithium hexamethyldisilylamide (LHMDS), organolithiums and Grignard reagents were obtained from Aldrich Chemical Co. or Acros Organics. Organolithiums and Grignard reagents were titrated before use by the method of Watson and Eastham.¹⁵⁴

Bis(hexafluoro-*tert*-butoxo)-2,6-diisopropylphenylimidoneophylidenemolybdenum(VI) (Schrock's catalyst) was purchased from Strem Chemicals Inc.

Dichlorobis(tricyclohexylphosphine)benzylideneruthenium(IV) (Grubbs' catalyst) was either purchased from Strem Chemicals Inc or prepared as detailed in **Section 7.4** of this chapter.

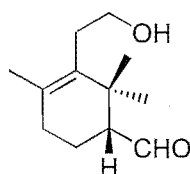
The high pressure Diels-Alder reactions described in **Section 7.6** were performed in a Psika High Pressure Reactor at the Australian National University, Canberra, Australia by Mr Tim O'Sullivan. The substrate was typically dissolved in a minimum volume of CH₂Cl₂ and then placed in a teflon container suspended in castor oil/MeOH. This container was then placed in the reactor for the period indicated at the pressure and temperature reported in the text.

7.2 Notes on Nomenclature

To allow some consistency within series of compounds, the naming of some compounds in this thesis differs from IUPAC nomenclature. In accord with the IUPAC recommendations in this situation¹⁵⁵ the naming systems used are described below.

Cyclohexene-based compounds described in **Chapters 2** and **3** have been named as derivatives of cyclohexene *irrespective of functional group*.

eg



IUPAC:

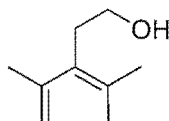
(±)-3-((2-Hydroxy)ethyl)-2,2,4-trimethylcyclohex-3-ene-(1*R**)-carbaldehyde

THIS THESIS:

(±)-(4*R**)-Formyl-2-((2-hydroxy)ethyl)-1,3,3-trimethylcyclohex-1-ene

Dienes described in **Chapters 2** and **4** have been named as diene derivatives *rather than as substituted alkenes*.

eg



IUPAC:

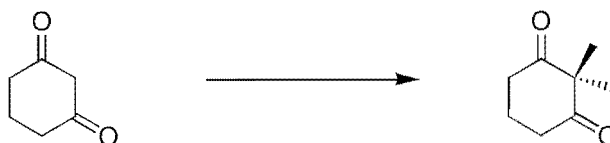
3-(Isopropylidene)-4-methyl-pent-4-en-1-ol

THIS THESIS:

3-(Hydroxyethyl)-2,4-dimethylpenta-1,3-diene

7.3 Experiments Described in Chapter 2

2,2-Dimethylcyclohexane-1,3-dione **2.5**



Cyclohexane-1,3-dione (5.00 g, 44.6 mmol), methyl iodide (6.11 mL, 98.1 mmol) and anhydrous K_2CO_3 (12.02 g, 87 mmol) in acetone (200 mL) were heated at reflux for 13 h. After cooling to 25 °C, the reaction was diluted with CH_2Cl_2 (100 mL), filtered, and the solvent removed *in vacuo* to yield a yellow oil. Purification by flash chromatography on silica (50% EtOAc – petroleum ether) gave **2.5** as an opaque solid (3.59 g, 57%).

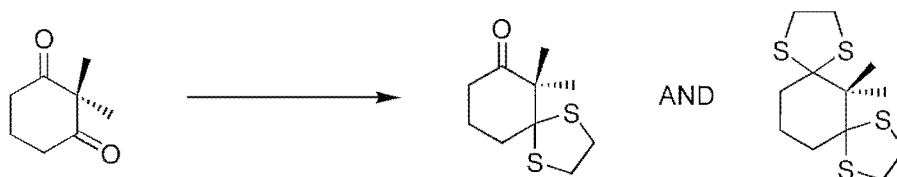
Mp 40-41 °C (lit¹⁵⁶ 39 °C)

1H nmr δ 1.32 (s, 6H), 1.97 (m, 2H), 2.71 (m, 4H)

^{13}C nmr δ 17.72, 21.90, 37.02, 61.40, 210.23.

LRMS (EI) calc. for $C_8H_{12}O_2$: 140.1; found: 140 [M^+]. The data was matched with the data for this compound from the WileyNBS library.

2,2-Dimethyl-3-(1,3-dithiolan-2-yl)cyclohexan-1-one **2.6** and 2-(2,2-Dimethyl-3-(1,3-dithiolan-2-yl)cyclohexyl)-1,3-dithiane **2.7**



Boron trifluoride diethyl etherate (3.40 mL, 27.5 mmol) was added to a solution of **2.5** (3.50 g, 25 mmol) in CH_2Cl_2 (125 mL) at 0 °C. Ethane-1,2-dithiol (2.20 mL, 26.2 mmol) in CH_2Cl_2 (125 mL) was added dropwise over 2 h. The reaction was allowed to warm to 25 °C. After stirring for 18 h the solvent was removed *in vacuo* to yield a pale yellow-orange oil. 1H NMR analysis showed a 4:1 mixture of the mono- and di-protected compounds. Purification by flash chromatography on silica (14% EtOAc –

petroleum ether) gave firstly **2.7** (0.77 g, 14%) and then **2.6** (3.59 g, 64%), both as oily solids.

Data for **2.6**

^1H nmr δ 1.35 (s, 6H), 1.98 (m, 2H), 2.42-2.50 (m, 4H), 3.27 (bs, 4H).

^{13}C nmr δ 22.98, 23.68, 36.46, 39.56, 39.82, 55.81, 78.82, 211.90.

FTIR (CDCl_3 , cm^{-1}) 1118.6, 1191.9, 1280.6, 1361.7, 1382.9, 1425.3, 1465.8, 1705.0, 2925.8.

HRMS (EI) calc. for $\text{C}_{10}\text{H}_{16}\text{OS}_2$: 216.06426; found: 216.06454.

Anal. calc. for $\text{C}_{10}\text{H}_{16}\text{OS}_2$: C 55.51, H 7.45; found C 55.43, H 7.51.

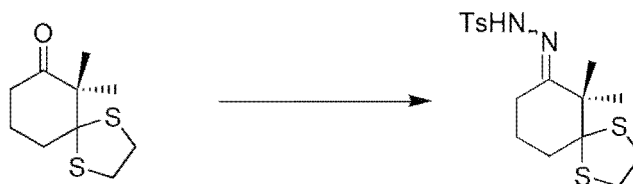
Selected data for **2.7**:

^1H nmr δ 1.55 (s, 6H), 1.83 (bs, 2H), 2.18 (bs, 4H), 3.22 (bs, 4H)

^{13}C nmr δ 22-28 (b, 1C), 24.51, 38-42 (b, 1C), 41.14, 48.94, 80.12.

HRMS (EI) calc. for $\text{C}_{12}\text{H}_{20}\text{S}_4$: 292.04479; found: 292.04442.

2,2-Dimethyl-3-(1,3-dithiolan-2-yl)cyclohexan-1-one tosyl hydrazone **2.8**



The ketone **2.6** (1.00 g, 4.62 mmol) and tosylhydrazide (1.03 g, 5.55 mmol) in EtOH (6 mL) were heated at reflux for 2 h. After cooling to 25 °C, the solvent was removed *in vacuo* to give an oily white solid. Trituration with EtOH, followed by filtration gave **2.8** as a white solid (1.96 g, 92%).

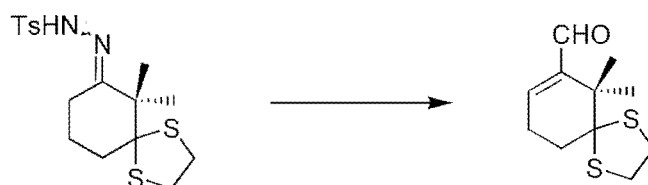
Mp 125-127 °C.

^1H nmr δ 1.28 (s, 6H), 1.73 (m, 2H), 2.22-2.29 (m, 4H), 2.42 (s, 3H), 3.18 (bs, 4H), 7.30 (d, 2H, $J = 8.3$ Hz), 7.49 (bs, 1H, NH), 7.85 (d, 2H, $J = 8.3$ Hz)

^{13}C nmr δ 21.55, 21.60, 23.66, 24.21, 39.73 (3C by 2D experiments), 49.48, 79.26, 128.21, 129.31, 135.22, 143.72, 163.66.

FTIR (CDCl_3 , cm^{-1}) 1166.9, 1334.6, 1382.9, 2927.7.

LRMS (FAB, NOBA) calc. for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2\text{S}_3$: 384.1; found: 385.1 [$\text{M} + 1$].

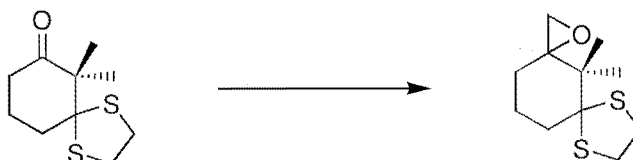
3,3-Dimethyl-3-(1,3-dithiolan-2-yl)-2-formylcyclohex-1-ene 2.9

The hydrazone (150 mg, 0.39 mmol) was dissolved in freshly distilled TMEDA (3.5 mL) and was cooled to -78°C . *n*-Butyllithium (1.11 mL of 1.60 M in hexanes, 1.78 mmol) was added dropwise, to give a bright orange-red solution. The cooling bath was removed and the reaction was allowed to warm to 25°C . After stirring for 5 min at 25°C , DMF (0.36 mL, 4.72 mmol) was added dropwise. The pale yellow solution that resulted was stirred for 5 min and then poured into saturated aqueous NH_4Cl . The mixture was extracted with EtOAc-petroleum ether (1:1, 2 x 25 mL) and the combined organic phases were dried (MgSO_4), filtered, and the solvent removed *in vacuo* to yield a pale brown oil. Purification by flash chromatography (11% EtOAc – petroleum ether) gave **2.9** (60 mg, 67%). ^1H nmr analysis indicated the presence of the corresponding cyclohexene (*ca* 10%). The two compounds were not separable.

Selected data for 2.9

^1H nmr δ 1.46 (s, 6H), 3.25 (s, 4H), 6.66 (t, 1H, $J = 3.4$ Hz), 9.32 (s, 1H).

HRMS (EI) calc. for $\text{C}_{11}\text{H}_{16}\text{OS}_2$: 228.06426; found: 228.06429.

(±)-2-(2,2-Dimethyl-3-(1,3-dithiolan-2-yl)cyclohexyl) oxirane 2.10

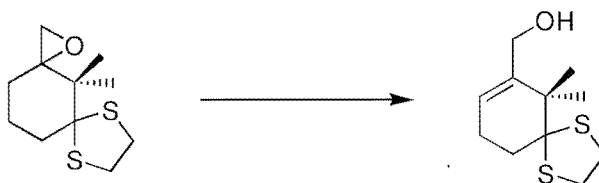
Sodium hydride (1.414 g of 80% dispersion in oil, 47.1 mmol) was washed with petroleum ether (2 x 10 mL) and dried under an N₂ stream. DMSO (20 mL) was added, followed by trimethyloxosulfonium iodide (10.71 g, 48.7 mmol). The mixture was stirred at 25 °C for 2 h and then the ketone (3.40 g, 15.7 mmol) in DMSO (5 mL) was added and the reaction was heated to 40 °C for 6 h. The reaction was quenched by pouring into H₂O (50 mL) followed by extraction with EtOAc (3 x 50 mL). The combined organic extracts were washed with saturated brine (2 x 50 mL), dried (MgSO₄), filtered, and the solvent removed *in vacuo* to yield a pale yellow oil (3.44 g, 95%). ¹H NMR analysis indicated the oil to be essentially pure epoxide **2.10**.

¹H nmr δ 1.11 (s, 3H), 1.22 (s, 3H), 1.74-1.96 (m, 4H), 2.05-2.18 (m, 1H), 2.29-2.40 (m, 1H), 2.48 (d, 1H, *J* = 4.4 Hz), 2.92 (d, 1H, *J* = 4.9 Hz), 3.18-3.28 (m, 4H).

¹³C nmr δ 20.52 (bs, 1C), 21.83 (bs, 1C), 23.08, 29.94, 38.72, 39.37, 40.50, 43.71, 52.13 (bs, 1C), 62.36, 79.06.

FTIR (CDCl₃, cm⁻¹) 1114.9, 1191.9, 1280.6, 1359.2, 1383.1, 1423.3, 1466.8, 2947.1.

HRMS (EI) calc. for C₁₁H₁₈OS₂: 230.07991; found: 230.07989.

4-(1,3-Dithiolan-2-yl)-2-(hydroxymethyl)-3,3-dimethylcyclohex-1-ene 2.11

A solution of trimethylsilyl triflate (TMSOTf) (0.033 mL, 0.17 mmol) and 2,6-lutidine (0.020 mL, 0.17 mmol) in PhMe (0.5 mL) was added dropwise over a period of 10 min to a solution of the epoxide **2.10** (40 mg, 0.17 mmol) in PhMe (1.5 mL) at -78 °C. The reaction was stirred at -78 °C for 10 min and then allowed to warm to 25 °C. The

reaction was poured into cold H₂O (20 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were shaken for *ca* 1 min with 5% HCA (50 mL) to remove the trimethylsilyl group. The layers were separated and the organic phase was washed with saturated NaHCO₃ (2 x 20 mL), brine (2 x 20 mL), then dried (MgSO₄), filtered, and the solvent removed *in vacuo* to yield a pale yellow oil. Purification by flash chromatography on silica (33% EtOAc – petroleum ether) gave firstly returned starting material (11mg) and then **2.11** as a colorless oil (24 mg, 83% on returned starting material). On a larger scale (13 mmol) the yield of this reaction was 49%.

¹H nmr δ 1.34 (bs, 6H), 2.31 (bs, 4H), 3.22 (s, 4H), 4.10 (bs, 2H), 5.65 (bs, 2H).

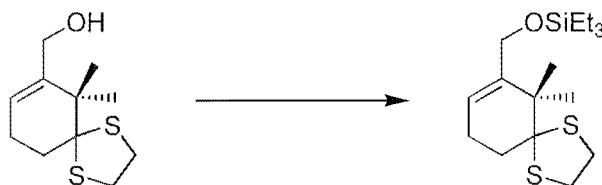
¹³C nmr δ 24.64, 25.14, 36.68, 39.26, 42.77, 64.43, 78.08, 123.09, 144.21.

FTIR (CDCl₃, cm⁻¹) 1118.6, 1191.9, 1280.6, 1361.7, 1382.9, 1425.3, 1465.8, 2925.8, 2976.0, 3200.

HRMS (EI) calc. for C₁₁H₁₈OS₂: 230.07991; found: 230.08007.

Anal. calc. for C₁₁H₁₈OS₂: C 57.34, H 7.87, S 27.84; found: C 57.06, H 7.96, S 28.17.

4-(1,3-Dithiolan-2-yl)-2-((triethylsilyloxy)methyl)-3,3-dimethylcyclohex-1-ene **2.12**

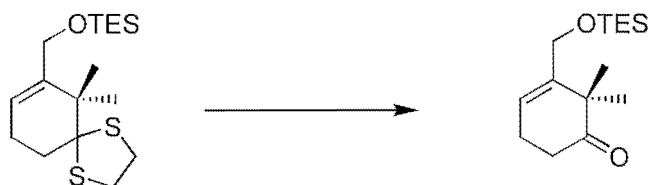


A solution of the alcohol **2.11** (1.46g, 6.3 mmol) in CH₂Cl₂ (50 mL) was cooled to -78 °C and treated with Et₃N (4.40 mL, 31.7 mmol) and trimethylsilyl triflate (Test) (1.57 mL, 6.96 mmol). The reaction was stirred at -78 °C for 1 h at which point TLC showed no starting material to be present. Saturated aqueous NaHCO₃ (20 mL) was added and the reaction was poured into diethyl ether - saturated aqueous NaHCO₃ (1:1, 50 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 20 mL). The combined organic phases were washed with brine (50 mL), dried (MgSO₄), filtered, and the solvent removed *in vacuo* to yield a pale yellow oil. Attempted purification by flash chromatography on silica (17% EtOAc – petroleum

ether) gave **2.12** as a colorless oil (1.81 g, 83%), which contained 10 % of silyl impurities by ^1H nmr. This compound was used without further purification.

^1H nmr δ 0.62 (m, 6H), 0.96 (m, 9H), 1.33 (s, 6H), 2.31 (bs, 4H), 3.22 (s, 4H), 4.12 (bs, 2H), 5.65 (bs, 1H).

4-Oxo-2-((triethylsilyloxy)methyl)-3,3-dimethylcyclohex-1-ene **2.13**



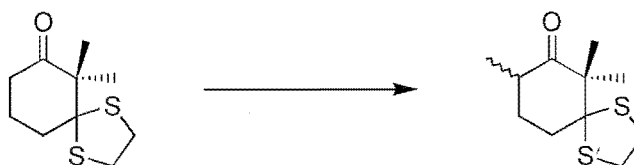
The thioacetal **2.12** (500 mg, 1.45 mmol) in MeCN (1 mL) was added to a well-stirred solution of AgNO_3 (1.11g, 6.53 mmol), *N*-chlorosuccinimide (800mg, 5.80 mmol) and 2,6-lutidine (1.69 mL, 1.45 mmol) in 80% aqueous acetonitrile (9 mL) at 0 °C. After stirring for 5 min, saturated aqueous Na_2SO_3 (1 mL), then saturated aqueous NaHCO_3 (1 mL) and finally brine (1 mL) were added at 1 min intervals. The reaction was then poured into 1:1 petroleum ether – CH_2Cl_2 (50 mL) and filtered. The layers were separated and the aqueous phase was extracted with 1:1 petroleum ether – CH_2Cl_2 (2 x 10 mL). The combined organic phases were washed with brine (50 mL), dried (MgSO_4), filtered, and the solvent removed *in vacuo* to yield a pale yellow oil. Purification by flash chromatography on silica (17% EtOAc – petroleum ether) gave **2.13** as a colorless oil (274 mg, 58% over two steps.)

^1H nmr δ 0.65 (m, 6H), 0.98 (t, 9H, $J = 7.8$ Hz), 1.23 (s, 6H), 2.42-2.57 (m, 4H), 4.16 (m, 2H), 5.90 (m, 1H).

^{13}C nmr δ 4.45, 6.83, 24.19, 24.33, 24.65, 35.49, 46.61, 62.32, 120.67, 142.92, 214.93.

FTIR (CDCl_3 , cm^{-1}) 1118.6, 1189.4, 1280.6, 1357.4, 1383.2, 1425.3, 1708.4, 2947.9.

HRMS (EI) calc. for $\text{C}_{15}\text{H}_{28}\text{O}_2\text{Si}$: 268.18586; found: 268.18583.

3-(1,3-Dithiolan-2-yl)-2,2,6-trimethylcyclohexan-1-one 2.14

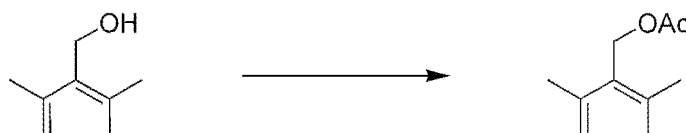
A solution of the ketone **2.6** (740 mg, 4 mmol) in THF (5 mL) was added to a solution of lithium diisopropylamide (2.6 mL of 2.0 M in heptane/THF/PhEt, 5.2 mmol) in THF (15 mL) at -78 °C. After stirring at -78 °C for 20 min, methyl iodide (0.750 mL, 12 mmol) was added dropwise. The reaction was allowed to warm, with stirring, from -78 °C to 25 °C over a period of 2.5 h. The reaction was then poured into saturated aqueous NH₄Cl (50 mL) and extracted with diethyl ether (2 x 50 mL). The combined organic phases were washed with brine, dried (MgSO₄), filtered, and the solvent removed *in vacuo* to yield a pale yellow oil. Purification by flash chromatography (14% EtOAc – petroleum ether) gave **2.14** (594 mg, 65%) as a pale yellow oil.

¹H nmr δ 1.01 (d, 3H, *J* = 6.4 Hz), 1.32 (s, 3H), 1.36 (s, 3H), 1.50-1.67 (m, 1H), 1.98-2.07 (m, 1H), 2.17 (dq, 1H, *J* = 3.9, 6.8, 14.2 Hz), 2.70-2.82 (m, 2H), 3.19-3.30 (m, 4H).

¹³C nmr δ 14.88, 20.81, 25.81, 32.87, 39.16, 39.28, 39.95, 40.22, 41.1, 79.36, 213.03.

FTIR (CDCl₃, cm⁻¹) 1191.9, 1281.2, 1361.4, 1382.7, 1700.2, 2927.1

HRMS (EI) calc. for C₁₁H₁₈OS₂: 230.07990; found: 230.08010.

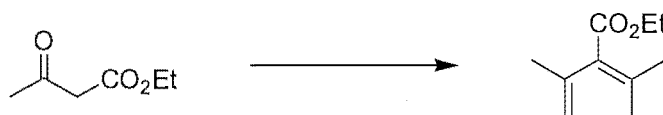
3-((Acetoxy)methyl)-2,4-dimethylpenta-1,3-diene 2.18

A solution of the alcohol (800 mg, 6.34 mmol) and DMAP (155 mg, 1.27 mmol) in CH₂Cl₂ (10 mL) was cooled to 0 °C and was treated sequentially with Et₃N (1.06 mL, 7.61 mmol), and Ac₂O (0.658 mL, 6.97 mmol). The reaction was allowed to warm to room temperature and was stirred for 1 h. H₂O (10 mL) was added and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ (2 x 10 mL), and the

combined organic phases were washed with saturated aqueous NH_4Cl , saturated aqueous NaHCO_3 , and brine (20 mL). The combined organic phases were dried (MgSO_4), filtered, and the solvent removed *in vacuo* to give a pale yellow oil. Purification by flash chromatography (5% diethyl ether – petroleum ether) gave **2.18** as a clear oil (896 mg, 84%).

^1H nmr δ 1.72 (s, 3H), 1.76 (s, 3H), 1.78 (3H, d, $J = 1.5$ Hz), 2.02 s (3H), 4.64 (bs, 3H), 4.94 (m, 1H, $J = 1.5, 2.5$ Hz).

3-(Ethoxycarbonyl)-2,4-dimethylpenta-1,3-diene 2.19



Ethylacetoacetate (130g, 0.98 mol), acetone (107 mL, 1.96 mol), acetic anhydride (107 mL, 1.16 mol) and ZnCl_2 (19 g, 0.14 mol) were heated at reflux for 72 h. The deep red-brown solution was cooled to 25 °C and PhH (100 mL) was added. The organic phase was washed with H_2O (6 x 25 mL) and the combined aqueous phases were extracted with PhH (2 x 50 mL). The combined organic phases were dried (MgSO_4), filtered, and the solvent removed *in vacuo*. Distillation at reduced pressure gave the desired ketone (49.5 g, 30%).

Bp 40 °C @ 0.1 mmHg.

^1H nmr δ 1.27 (t, 3H, $J = 6.8$ Hz), 1.93 (s, 3H), 2.07 (s, 3H), 2.26 (s, 3H), 4.22 (q, 2H, $J = 7.3$ Hz).

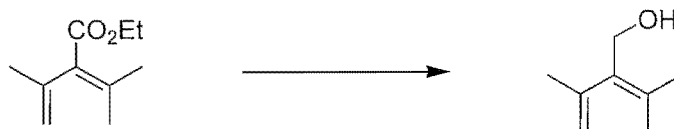
A solution of methylmagnesium iodide (*ca* 0.49 mol in 200 mL diethyl ether) was prepared under standard Grignard conditions. After aging at reflux for 1 h, this solution was cooled to 25 °C and was added by cannula over *ca* 45 min to a solution of the ketone (65.0 g, 0.41 mol) in diethyl ether (400 mL) at 0 °C. The reaction was allowed to warm from 0 °C to 25 °C and was stirred for 8 h. The light yellow solution was cooled to 0 °C and quenched by careful addition of saturated aqueous NH_4Cl (200 mL).

The layers were separated and the organic phase was washed with H₂O (2 x 50 mL) and brine (50 mL), then dried (MgSO₄), filtered, and the solvent removed *in vacuo* to yield a yellow-white oil (78g). This oil was dissolved in PhH (200 mL) and treated with *p*-TsOH (15.38 g, 0.078 mol). The reaction was heated to 65 °C for 3 h and then cooled to 25 °C. Et₃N (11.1 mL, 0.079 mol) was added along with diethyl ether (200 mL). The organic phase was washed with H₂O (140 mL), saturated aqueous NaHCO₃ (140 mL) and brine (140 mL), then dried (MgSO₄), filtered, and the solvent removed *in vacuo*. Distillation at reduced pressure gave **2.11** (44.1 g, *ca* 65%). ¹H NMR analysis showed the product to be *ca* 90% pure. This compound was used without further purification.

Bp 45-55 °C @ 0.2 mmHg (lit³⁰ 40-45 °C @ 0.2 mmHg)

¹H nmr δ 1.18 (t, 3H, *J* = 7.5 Hz), 1.73 (s, 3H), 1.75 (s, 3H), 1.91 (s, 3H), 4.10 (q, 2H, *J* = 7.0 Hz), 4.67 (bd, 1H, *J* = 1.0 Hz), 4.99 (bd, 1H, *J* = 1.0 Hz).

3-(Hydroxymethyl)-2,4-dimethylpenta-1,3-diene **2.20**



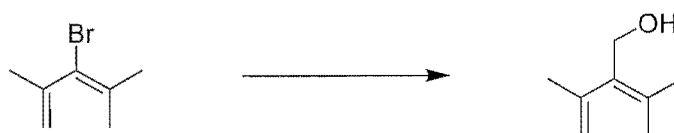
A solution of the diene ester (1.00 g, 5.9 mmol) in diethyl ether (6 mL) was added to a suspension of LiAlH₄ (224 mg, 5.9 mmol) in diethyl ether (3 mL) at -15 °C. The reaction was stirred, with warming from -15 °C to 0 °C over a period of 2 h before being quenched by the addition of EtOAc (3 mL) and then saturated aqueous Na₂SO₄ (5 mL). The precipitate was filtered off and washed with EtOAc (3 x 10 mL). The combined organic layer was dried (MgSO₄), filtered, and the solvent removed *in vacuo* to yield a colorless oil (650 mg, 87%).

This material was used without further purification, as ^1H nmr analysis showed it to be > 95% pure.

^1H nmr³⁰ δ 1.70 (s, 3H), 1.75 (s, 3H), 1.81 (t, 3H, $J = 0.9$ Hz), 4.15 (d, 2H, $J = 35.8$ Hz), 4.69 (m, 1H), 5.05 (m, 1H).

3-(Hydroxymethyl)-2,4-dimethylpenta-1,3-diene 2.20

Alternative preparation from the bromodiene



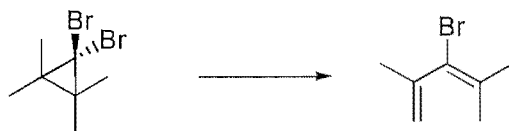
tert-Butyllithium (11.97 mL of 1.67 M in pentane, 20 mmol) was added over *ca* 5 min to a solution of the bromodiene **2.21** (1.75 g, 10 mmol) in THF (40 mL) at -78 °C. After stirring for 15 min, DMF (3.10 mL, 40 mmol) was added and the reaction was allowed to stir from -78 °C to 25 °C over a period of 1 h. The reaction was quenched with saturated aqueous NH_4Cl (40 mL) and the layers were separated. The aqueous phase was extracted with diethyl ether (40 mL) and the combined organic phases were washed with brine (100mL), dried (MgSO_4), filtered, and the solvent removed *in vacuo* to yield a light orange oil. This oil was filtered through a short silica column with 14% EtOAc – petroleum ether to give the intermediate aldehyde as a colorless oil (1.05 g) contaminated with aliphatic impurities (*ca* 10%).

The aldehyde obtained above was dissolved in MeOH (21 mL) along with $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (3.17 g, 8.5 mmol). NaBH_4 (322 mg, 8.5 mmol) was added in one portion. There was a mild exotherm, gas was evolved and the reaction changed color to milky white. After stirring for 10 min saturated aqueous NH_4Cl (50 mL) was added and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 50 mL) and the combined organic phases were dried (MgSO_4), filtered, and the solvent removed *in vacuo* to give a pale yellow oil. Purification by flash chromatography on silica (25%

diethyl ether – petroleum ether) gave **2.20** as a colorless oil (727mg, 58% over two steps).

^1H nmr data are reported above.

3-Bromo-2,4-dimethylpenta-1,3-diene **2.21**



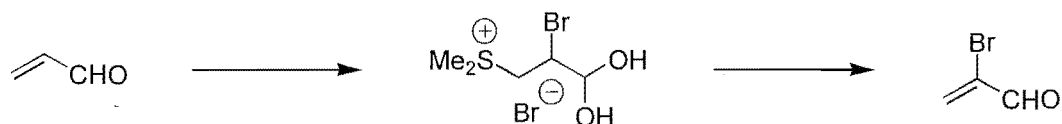
The dibromocyclopropane **2.24** (17.10 g, 66.80 mmol) was dissolved in *N,N*-dimethylaniline (15.0 mL) in a 100 mL round-bottom flask equipped with a dry ice-acetone condenser, an internal thermometer, and a CaCl_2 drying tube. The reaction was heated slowly (CAUTION) to approximately 140 °C (internal temperature) whereupon a vigorous exotherm occurred and the internal temperature rose to 175 °C. The heating bath was removed and the reaction was allowed to cool to 25 °C. The reaction was diluted with diethyl ether (150 mL) and washed with 6 M HCl (2 x 50 mL) and then brine (50 mL). The diethyl ether layer was dried (MgSO_4), filtered, and the solvent removed *in vacuo* to yield **2.21** as a pale yellow oil (11.20 g, 96%).

^1H nmr δ 1.81 (s, 3H), 1.89 (dd, 3H, $J = 1.0, 2.4$ Hz), 1.90 (s, 3H), 4.91 (dd 1H, $J = 1.4, 2.4$ Hz), 5.04 (dd, 1H, $J = 1.5, 3.4$ Hz).

^{13}C nmr δ 21.68, 21.79, 24.43, 116.45, 120.14, 130.96, 144.05.

FTIR (KBr plate, neat, cm^{-1}) 908.4, 983.6, 1078.1, 1276.8, 1369.4, 1442.7, 1716.5, 1762.8, 2916.2, 2977.9.

HRMS (EI) calc. for $\text{C}_7\text{H}_{11}^{81}\text{Br}$: 176.00250; found: 176.00213.

2-Bromoacrolein¹⁵⁷

Bromine (1.93 mL, 37.5 mmol) in CCl₄ (5 mL) was added dropwise to a solution of dimethylsulfide (5.0 mL, 68.1 mmol) in MeCN (100 mL) at -40 °C. The yellow precipitate that formed was stirred for 5 min and then acrolein (3.0 mL, 44.9 mmol) was added dropwise. This caused the precipitate to change white. After stirring for 15 min the reaction was diluted with diethyl ether (100 mL) and the precipitate was filtered off to yield 10.30g (93%) of the sulfonium salt as the dihydroxy acetal.

Mp 77 °C (lit¹⁵⁷ 78-9 °C).

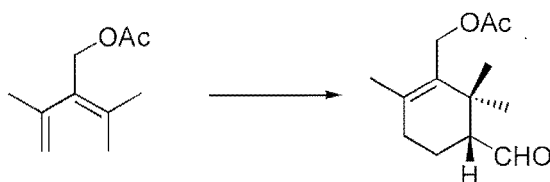
¹H nmr (D₂O) δ 2.99 (s, 3H), 3.03 (s, 3H), 3.93 (m, 2H), 4.43 (m, 2H), 5.24 (d, 1H, *J* = 3.5 Hz).

¹³C nmr (D₂O + 1% DMSO) δ 27.45, 27.93, 28.90, 50.48, 91.08.

MS (FAB, glycerol) calc. for C₅H₁₂BrO₂S: 215; found [M+1]: 216.

The sulfonium salt was suspended in H₂O (50 mL) containing NaHCO₃ (5.0g). The mixture was heated to 35 °C for 15 min and then cooled to 25 °C at which stage a biphasic system was observed. The top layer was separated, dried (MgSO₄), filtered, and diluted with CH₂Cl₂ (10 mL) containing hydroquinone (10 mg). Careful distillation at atmospheric pressure to remove the bulk of the volatiles (removal of all of the solvent resulted in polymerization) boiling at less than 60 °C gave the desired compound as a *ca* 1:1 mixture with CH₂Cl₂ (3.14 g, *ca* 30%).

¹H nmr¹⁵⁷ δ 6.90 (m, 2H), 9.25 (s, 1H).

(±)-2-(Acetoxymethyl)-(4*R)-formyl-1,3,3-trimethylcyclohex-1-ene 2.22**

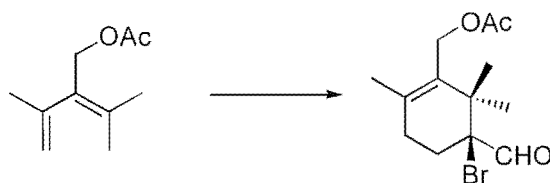
A solution of diene acetate **2.18** (1.68 g, 10 mmol) in CH₂Cl₂ (10 mL) was added to a -78 °C solution of acrolein (2.34 mL, 35 mmol) and BF₃·OEt₂ (3.59 mL, 30 mmol) in CH₂Cl₂ (50 mL). After stirring at -78 °C for 2 h, the reaction was poured into H₂O. The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (50 mL). The combined organic phases were washed with brine (2 x 50 mL), then dried (MgSO₄), filtered, and the solvent removed *in vacuo* to quantitatively yield a light brown oil. Purification by flash chromatography (25% diethyl ether – petroleum ether) gave **2.22** as a clear oil (1.64 g, 79%).

¹H nmr δ 1.04 (s, 3H), 1.20 (s, 3H), 1.69, (s, 3H), 1.71-1.89 (m, 2H), 2.04 (s, 3H), 2.10 (m, 2H), 2.20 (dt, 1H, *J* = 2.9, 10.2 Hz), 4.59 (s, 2H), 9.84 (d, 1H, *J* = 2.4Hz).

¹³C nmr δ 19.35, 19.74, 21.03, 23.48, 27.18, 30.79, 36.27, 57.03, 60.26, 131.54, 136.47, 171.26, 205.68.

FTIR (KBr plate, neat, cm⁻¹) 1023.8, 1242.3, 1365.6, 1720.9, 2935.5, 2968.2.

HRMS (EI) calc. for C₁₂H₁₇O₃ [M⁺ – CH₃]: 209.11777; found: 209.11679.

(±)-2-(Acetoxymethyl)-(4*S)-bromo-4-formyl-1,3,3-trimethylcyclohex-1-ene 2.23**

A solution of diene acetate **2.18** (168 mg, 1 mmol) in CH₂Cl₂ (1 mL) was added to a -78 °C solution of 2-bromoacrolein (950 mg of 1:1 with CH₂Cl₂, 3.5 mmol) and BF₃·OEt₂ (0.369 mL, 3 mmol) in CH₂Cl₂ (5 mL). After stirring at -78 °C for 2 h, the reaction was poured into H₂O, and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic phases were washed with brine (20 mL), then dried (MgSO₄), filtered, and the solvent

removed *in vacuo* to quantitatively yield a light yellow oil. Purification by flash chromatography (25% diethyl ether – petroleum ether) gave **2.23** as a clear oil (182 mg, 60%).

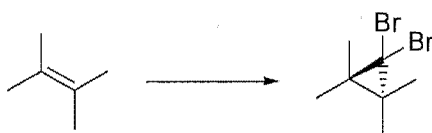
^1H nmr δ 1.23 (s, 3H), 1.36 (s, 3H), 1.73 (s, 3H), 2.05 (s, 3H), 2.19-2.36 (m, 4H), 4.64 (m, 2H), 9.66 (s, 1H).

^{13}C nmr δ 19.59, 21.06, 24.83, 26.10, 27.72, 30.56, 40.64, 60.59, 79.17, 129.27, 136.16, 171.09, 192.22.

FTIR (KBr plate, neat, cm^{-1}) 1024.8, 1242.9, 1367.1, 1721.2, 2978.2

HRMS (EI) calc. for $\text{C}_{11}\text{H}_{15}\text{BrO}$: 242.03063; found: 242.02981.

1,1-Dibromo-2,2,3,3-tetramethyl cyclopropane **2.24**



Bromoform (9.20 mL, 105.2 mmol) was added dropwise over 30 min to 2,3-dimethylbut-2-ene (14.12 mL, 116.8 mmol) and potassium *tert*-butoxide (23.60 g, 210.4 mmol) in pentane (100 mL) at 0 °C. The reaction was stirred at 0 °C for 4 h and then water (100 mL) was added. After warming to 25 °C, the pentane layer was separated, dried (MgSO_4), filtered, and the solvent removed *in vacuo* to yield **2.24** as a pale yellow solid (17.10 g, 64%).

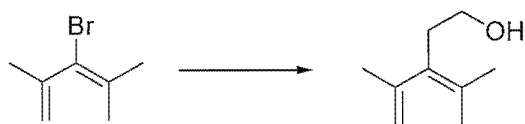
Mp 77 °C (lit¹⁵⁸ 82-83 °C).

^1H nmr δ 1.25 (s, 12H).

^{13}C nmr δ 21.72, 29.71, 58.85.

FTIR (CDCl_3 , cm^{-1}) 1110.9, 1379.0, 1456.4, 1460.0, 1473.5, 2871.8, 2925.8, 2958.6, 3010.7.

Anal. calc. for $\text{C}_7\text{H}_{12}\text{Br}_2$: C 32.85, H 4.73; found: C 32.87, H 4.68.

3-(Hydroxyethyl)-2,4-dimethylpenta-1,3-diene 2.25

tert-Butyllithium (67.2 mL of 1.7 M in pentane, 114.2 mmol) was added over a period of 10 min to a solution of diene **2.21** (10.00 g, 57.1 mmol) in THF (100 mL) at -78 °C. After stirring the red-brown solution for a further 10 min at -78 °C, ethylene oxide (14.3 mL, 285.5 mmol) was rapidly added, causing immediate decolorization of the reaction to pale yellow. The reaction was stirred, with warming from -78 °C to 0 °C over a period of 1 h, then poured into saturated aqueous NH₄Cl (200 mL) and extracted with diethyl ether (2 x 100 mL). The combined organic phases were washed with brine (200 mL), dried (MgSO₄), filtered, and the solvent removed *in vacuo* to quantitatively yield **2.25** as a light brown oil. Analysis by ¹H nmr indicated **2.25** to be > 95% pure.

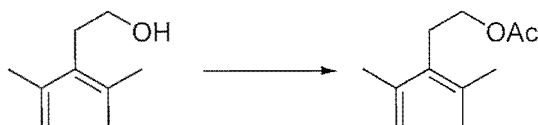
An analytical sample was obtained by flash chromatography on silica (25% diethyl ether – petroleum ether):

¹H nmr δ 1.68 (s, 3H), 1.70 (s, 3H), 1.75 (s, 3H), 2.37 (t, 2H, *J* = 6.9 Hz), 3.59 (t, 2H, *J* = 6.8 Hz), 4.56 (m, 1H), 4.96 (m, 1H).

¹³C nmr δ 19.78, 21.73, 22.45, 33.90, 61.15, 113.48, 128.36, 132.53, 146.34.

FTIR (CDCl₃, cm⁻¹) 1045.3, 1236.3, 1373.2, 1444.6, 2883.4, 2916.2, 2966.3, 3008.7, 3452.3, 3577.7.

HRMS (EI) calc. for C₉H₁₆O: 140.12012; found: 140.12017.

3-(Hydroxyethyl)-2,4-dimethylpenta-1,3-dienyl acetate 2.26

A solution of diene alcohol **2.25** (500 mg, 3.6 mmol) in CH₂Cl₂ (10 mL) at 0 °C was treated with DMAP (44 mg, 0.36 mmol) in CH₂Cl₂ (1 mL), triethylamine (0.600 mL,

4.3 mmol) and acetic anhydride (0.377 mL, 4.0 mmol). The reaction was stirred, with warming from 0 °C to 25 °C over 1 h. The reaction was diluted with CH₂Cl₂ (25 mL) and washed with saturated aqueous NaHCO₃ (2 x 25 mL), saturated aqueous NH₄Cl (2 x 25 mL) and brine (2 x 25 mL), then dried (MgSO₄), filtered, and the solvent removed *in vacuo* to yield a pale yellow oil. Purification by flash chromatography on silica (25% diethyl ether – petroleum ether) gave **2.26** as a clear oil (504 mg, 77%).

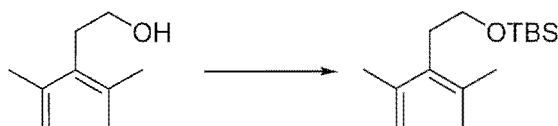
¹H nmr δ 1.66 (s, 3H), 1.69 (s, 3H), 1.76 (s, 3H), 2.02 (s, 3H), 2.41 (t, 2H, *J* = 7.8 Hz), 4.02 (t, 2H, *J* = 7.3 Hz), 4.56 (m, 1H), 4.94 (m, 1H).

¹³C nmr δ 19.74, 21.03, 21.71, 22.47, 30.20, 63.03, 113.78, 128.29, 131.79, 145.88, 171.13.

FTIR (CDCl₃, cm⁻¹) 1031.8, 1247.9, 1365.5, 1446.5, 1732.0, 2916.2, 2964.4.

HRMS (EI) calc. for C₉H₁₄ [M⁺ - AcOH]: 122.10955; found: 122.10957.

3-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-2,4-dimethylpenta-1,3-diene **2.27**



A solution of diene alcohol **2.25** (500 mg, 3.6 mmol) in DMF (1 mL) was added to a solution of *tert*-butyldimethylsilyl chloride (651 mg, 4.3 mmol) and imidazole (732 mg, 10.8 mmol) in DMF (1 mL) at 25 °C. The reaction was allowed to stir at 25 °C for 16 h. The reaction was diluted with EtOAc (20 mL) and washed with saturated aqueous NaHCO₃ (2 x 25 mL), saturated aqueous NH₄Cl (2 x 25 mL) and brine (2 x 25 mL), then dried (MgSO₄), filtered, and the solvent removed *in vacuo* to yield a pale yellow oil. Purification by flash chromatography on silica (10% EtOAc – petroleum ether) gave **2.27** as a clear oil (7.51 mg, 82%).

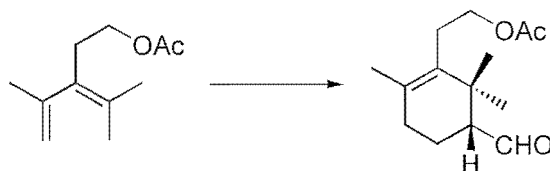
¹H nmr δ 0.05 (s, 6H), 0.89 (s, 9H), 1.66 (s, 3H), 1.69 (s, 3H), 1.76 (m, 3H), 2.34 (bt, 2H, *J* = 7.8 Hz), 3.56 (t, 2H, *J* = 7.8 Hz), 4.53 (m, 1H), 4.90 (m, 1H).

^{13}C nmr δ -5.23, 18.35, 19.84, 21.68, 22.59, 25.98, 34.80, 61.85, 113.08, 127.23, 132.80, 146.60.

FTIR (CDCl_3 , cm^{-1}) 1074.3, 1255.6, 1444.6, 1463.9, 1471.6, 2856.4, 2929.7, 2956.7.

HRMS (EI) calc. for $\text{C}_{14}\text{H}_{27}\text{OSi}$ [$\text{M}^+ - \text{CH}_3$]: 239.18312; found: 239.18321.

(\pm)-2-(2-Acetoxy)ethyl-(4*R)-formyl-1,3,3-trimethylcyclohex-1-ene 2.28**



A solution of diene acetate **2.26** (400 mg, 2.19 mmol) in CH_2Cl_2 (1 mL) was added to a -78°C solution of acrolein (0.512 mL, 7.67 mmol) and $\text{BF}_3\cdot\text{OEt}_2$ (0.810 mL, 6.58 mmol) in CH_2Cl_2 (10 mL). After stirring at -78°C for 45 min, the reaction was diluted with CH_2Cl_2 (10 mL) and poured into diethyl ether- H_2O (1:1, 20 mL). The organic phase was separated, washed with saturated aqueous NaHCO_3 (20 mL), saturated aqueous NH_4Cl (20 mL) and brine (20 mL), then dried (MgSO_4), filtered, and the solvent removed *in vacuo* to quantitatively yield **2.28** as a light red oil.

An analytical sample was obtained by flash chromatography on silica (17% EtOAc – petroleum ether):

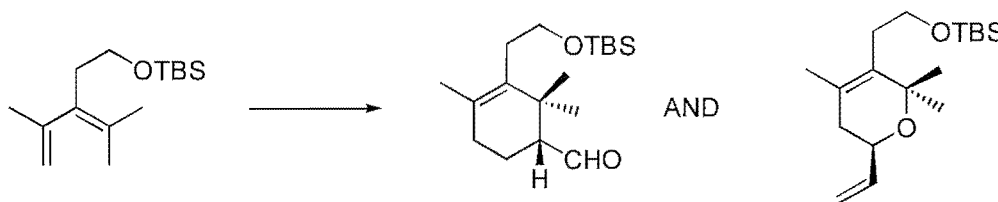
^1H nmr δ 1.06 (s, 3H), 1.23 (s, 3H), 1.69 (s, 3H), 1.71-1.89 (m, 2H), 2.03 (m, 2H), 2.05 (s, 3H), 2.15 (dt, 1H, $J = 3.0, 10.3$ Hz), 2.39 (m, 2H), 4.02 (m, 2H), 9.82 (d, 1H, $J = 3.0$ Hz).

^{13}C nmr δ 19.57, 20.09, 21.03, 23.32, 27.35, 27.54, 30.61, 36.90, 57.44, 63.68, 130.61, 131.71, 170.98, 206.01.

FTIR (CDCl_3 , cm^{-1}) 1031.8, 1242.1, 1365.5, 1386.7, 1720.4, 2935.5, 2968.2.

HRMS (EI) calc. for $\text{C}_{14}\text{H}_{22}\text{O}_3$: 238.15689; found: 238.15607.

(±)-2-((2-*tert*-Butyldimethylsilyloxy)ethyl)-(4*RS*)-formyl-1,3,3-trimethylcyclohex-1-ene **2.29** and (±)-3-(2-*tert*-Butyldimethylsilyloxyethyl)-2,2,4-trimethyl-(6*RS*)-ethenyl-5,6-dihydro-2*H*-pyran **2.30**



BF₃·OEt₂ (0.117 mL, 1.75 mmol) was added to a solution of the diene **2.27** (127 mg, 0.50 mmol) and acrolein (0.100 mL, 1.5 mmol) in CH₂Cl₂ (2 mL) at -78°C. The reaction was stirred at -78 °C for 1 h and then saturated NaHCO₃ (5 mL) was added. The reaction was then diluted with diethyl ether (20 mL). The layers were separated and the organic phase was washed with brine (20 mL), dried (MgSO₄), filtered, and the solvent removed *in vacuo* to yield a clear oil. Purification by flash chromatography on silica (10% diethyl ether – petroleum ether) gave firstly pyran **2.30** as a clear oil (33 mg, 21%) and then aldehyde **2.29** (88 mg, 57%).

Data for the pyran:

¹H nmr δ 0.07 (s, 6H), 0.90 (s, 9H), 1.29 (s, 6H), 1.68 (s, 3H), 1.79 (dd, 1H, *J* = 3.4, 17.1 Hz), 2.04-2.13 (m, 1H), 2.27 (t, 2H, *J* = 8.8 Hz), 3.53-3.65 (m, 2H), 4.12 (m, 1H), 5.12 (dt, 1H, *J* = 1.5, 10.8 Hz), 5.25 (dt, 1H, *J* = 1.5, 17.6 Hz), 5.89 (ddd, 1H, *J* = 5.9, 10.3, 17.1 Hz).

¹³C nmr δ -5.18, 18.40, 19.60, 25.03, 26.00, 28.51, 32.92, 37.22, 62.42, 68.89, 75.95, 115.08, 126.55, 132.18, 139.41.

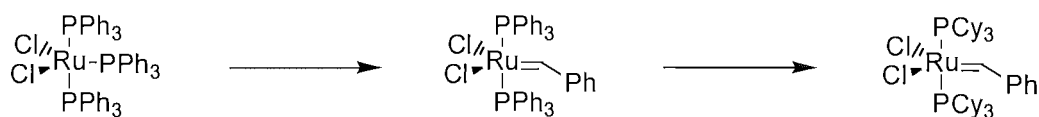
FTIR (CDCl₃, cm⁻¹) 1092.4, 1256.3, 1361.0, 1467.9, 2921.3.

HRMS (EI) calc. for C₁₇H₃₁O₂Si [*M*⁺ - CH₃]: 295.20933; found: 295.20921.

Data for the aldehyde are presented in **Section 7.4**.

7.4 Experiments Described in Chapter 3

Dichlorobis(tricyclohexylphosphine)benzylidene ruthenium(IV) (Grubbs' catalyst) 3.3¹⁵⁹



Preparation of phenyldiazomethane

A hydrocarbon solution of phenyldiazomethane was prepared by placing benzaldehyde tosylhydrazone (2.86 g, 10.40 mmol) and benzyltriethylammonium chloride (1.5 g) in a 250 mL round-bottom flask equipped with a stir-bar and reflux condenser. Petroleum ether (22 mL) and PhMe (4 mL) were added followed by 15 wt% aqueous NaOH (85 mL). The mixture was heated and vigorously stirred at *ca* 70 °C (moderate reflux) for 2 h. After 2 h the aqueous phase was clear and colorless and the organic phase was a deep red color. The mixture was poured into a 250 mL separatory funnel half-filled with ice. The mixture was shaken with venting until all of the ice had melted. The aqueous phase was discarded and the organic phase was washed twice with H₂O (100 mL). The organic phase was dried over Na₂SO₄, decanted into a 100 mL round-bottom flask, sealed with a septum, and degassed by sparging for 10 min with Ar. This solution can be stored indefinitely at -50 °C or for several hours at 0 °C.

Catalyst Synthesis

CH₂Cl₂ (140 mL) in a 250 mL three-neck round-bottom flask was sparged with Ar for 10 minutes and dichlorotris(triphenylphosphine)ruthenium(II) (3.90 g, 4.07 mmol) was added under Ar flush. The solution was stirred to dissolve the dark brown solid and then cooled to -50 °C. The phenyldiazomethane solution prepared above was cooled to 0 °C and added *via* polyethylene cannula to the solution of the dichlorotris(triphenylphosphine)ruthenium(II) over *ca* 10-15 minutes. After the

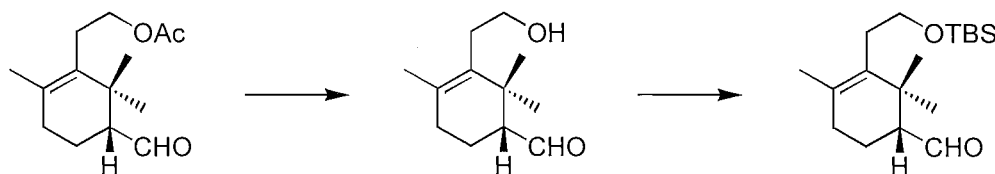
addition was complete, the reaction was allowed to warm to -20 °C and tricyclohexylphosphine (2.51 g, 8.95 mmol) was added *via* a solid addition funnel over *ca* 5-10 min. The mixture was warmed to room temperature and was a deep purple color at this point. Most of the solvent was removed on a rotary evaporator, leaving a dark purple slurry. Methanol (200 mL, degassed by 3 x freeze-pump-thaw cycles) was added which caused precipitation of a purple solid. This suspension was filtered on a No. 4 glass frit in the air. The solid was washed with methanol (3 x 100 mL) and then by acetone (3 x 75 mL). The purple solid obtained was dried under vacuum to give the title compound (3.10 g, 93%). ^1H NMR analysis showed the catalyst to be *ca* 90% pure. The major impurities are in the aromatic region and may be residual triphenylphosphine.[¶]

^1H nmr¹⁵⁹ (CD_2Cl_2) δ 1.25-1.77 (m, 30H), 2.58-2.62 (m, 3H), 7.33-7.56 (m, 3H), 8.44 (d, 2H, $J = 7.6\text{Hz}$), 20.02 (s, 1H, Ru=CH).

The catalyst should be stored in a Schlenk tube under Ar. The author has not observed any loss of activity over a period of one year when the catalyst is carefully stored.

[¶] This is in keeping with the findings of Grubbs and co-workers. The catalyst can be purified by dissolution in degassed dichloromethane followed by filtration through Celite[®]. Most of the solvent is removed under vacuum and the catalyst is precipitated by addition of methanol. The precipitated catalyst is isolated by filtration in the air and washing with methanol followed by acetone. R. H. Grubbs, personal communication.

(±)-2-((2-*tert*-Butyldimethylsilyloxy)ethyl)-(4*R)-formyl-1,3,3-trimethylcyclohex-1-ene 2.29**



The aldehyde **2.27** (11.32 g, 47.19 mmol) and potassium carbonate (13.04 g, 94.38 mmol) in MeOH-H₂O (9:1, 300 mL) were stirred at 25 °C for 40 min. The bulk of the MeOH was then removed *in vacuo* and the aqueous residue was extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with saturated aqueous NaHCO₃ (100 mL) and brine (100 mL), then dried (MgSO₄), filtered, and the solvent removed *in vacuo* to yield the crude alcohol as a pale yellow oil (9.12 g).

An analytical sample was obtained by flash chromatography on silica (25% EtOAc – petroleum ether):

¹H nmr δ 1.05 (s, 3H), 1.20 (s, 3H), 1.66 (s, 3H), 1.68-1.83 (m, 2H), 2.01 (m, 2H), 2.16 (dt, 1H, *J* = 3.0, 10.3 Hz), 2.39 (m, 2H), 4.02 (m, 2H), 9.82 (d, 1H, *J* = 3.0 Hz).

¹³C nmr δ 19.59, 20.16, 23.50, 27.74, 30.51, 31.66, 36.82, 57.51, 62.36, 129.87, 132.25, 206.24.

FTIR (CDCl₃, cm⁻¹) 1022.2, 1367.4, 1386.7, 1460.0, 1471.6, 1712.7, 2250.8, 2837.1, 2895.0, 2941.2, 3622.1.

HRMS (EI) calc. for C₁₂H₂₀O₂: 196.14633; found: 196.14603.

The crude alcohol in DMF (15 mL) was added to a solution of *tert*-butyldimethylsilyl chloride (8.54 g, 56.63 mmol) and imidazole (8.03 g, 117.57 mmol) in DMF (5 mL) at 25 °C. After stirring at 25 °C for 24 h the reaction was diluted with EtOAc (50 mL) and poured into H₂O (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with saturated aqueous NaHCO₃ (2 x 200 mL), saturated aqueous NH₄Cl (2 x 200 mL) and brine (200 mL), then dried (MgSO₄), filtered, and the solvent removed *in vacuo* to yield **2.29** as a pale yellow oil.

An analytical sample was obtained by flash chromatography on silica (10% diethyl ether – petroleum ether):

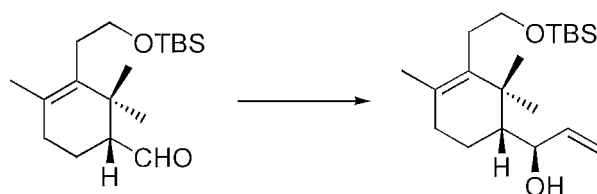
^1H nmr δ 0.07 (s, 6H), 0.91 (s, 9H), 1.05 (s, 3H), 1.20 (s, 3H), 1.66 (s, 3H), 1.73-1.88 (m, 2H), 2.01 (m, 2H), 2.15 (dt, 1H, $J = 3.4, 10.2$ Hz), 2.31 (m, 2H), 3.57 (m, 2H), 9.83 (d, 1H, $J = 3.0$ Hz).

^{13}C nmr δ -5.15, 18.39, 19.69, 20.21, 23.49, 26.02, 27.69, 30.56, 32.05, 36.86, 57.58, 62.84, 129.44, 132.74, 206.39.

FTIR (CDCl_3 , cm^{-1}) 1078.1, 1257.5, 1463.9, 1471.6, 1720.4, 2858.3, 2931.6, 2956.7.

HRMS (EI) calc. for $\text{C}_{17}\text{H}_{31}\text{O}_2\text{Si}$ [$\text{M}^+ - \text{CH}_3$]: 295.20933; found: 295.20896.

(\pm)-2-((2-*tert*-Butyldimethylsilyloxy)ethyl)-(4*R)-((1*R**)-hydroxyprop-2-enyl)-1,3,3-trimethylcyclohex-1-ene **3.11****



Vinylmagnesium bromide (12.0 mL of 1.0 M in THF, 12 mmol) was added to a solution of the aldehyde **2.29** (3.10 g, 10 mmol) in THF (200 mL) at -78°C . The reaction was allowed to stir from -78°C to -20°C over a period of 1 h. The reaction was poured into diethyl ether-saturated aqueous NH_4Cl (1:1, 200 mL) and the layers separated. The aqueous layer was extracted with diethyl ether (2 x 100 mL) and the combined organic phases were washed with brine (200 mL), dried (MgSO_4), filtered, and the solvent removed *in vacuo* to yield a pale yellow oil. Purification by flash chromatography on silica (10% EtOAc – petroleum ether) gave **3.11** as a clear oil (1.79g, 53% over 4 steps). Only one diastereoisomer could be detected by ^1H NMR analysis.

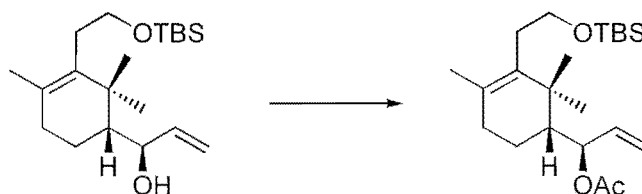
^1H nmr δ 0.06 (s, 6H), 0.90 (s, 9H), 1.06 (s, 3H), 1.07 (s, 3H), 1.32 (m, 1H), 1.52-1.61 (m, 2H), 1.64 (s, 3H), 1.96 (m, 2H), 2.31 (m, 2H), 3.58 (m, 2H), 4.48 (bd, 1H, $J = 2.9$ Hz), 5.12 (m, 1H), 5.25 (m, 1H), 5.83-5.94 (m, 1H).

^{13}C nmr δ -5.14, 17.52, 18.40, 20.35, 22.94, 26.05, 27.58, 32.36, 32.68, 38.13, 49.56, 62.99, 71.62, 113.30, 129.65, 133.74, 141.80.

FTIR (CDCl_3 , cm^{-1}) 1068.5, 1255.6, 1471.6, 2931.6, 2956.7, 3020.3, 3600.0.

HRMS (EI) calc. for $\text{C}_{20}\text{H}_{36}\text{OSi}$ [$\text{M}^+ - \text{H}_2\text{O}$]: 320.25355; found: 320.25304.

(\pm)-(4*R)-((1*R**)-(Acetoxy)prop-2-enyl)-2-((2-*tert*-butyldimethylsilyloxy)ethyl)-1,3,3-trimethylcyclohex-1-ene 3.12**



A solution of alcohol **3.11** (1.07 g, 3.16 mmol), DMAP (38 mg, 0.32 mmol), and Hünig's base (0.660 mL, 3.79 mmol) in CH_2Cl_2 (80 mL) at 0 °C was treated with acetic anhydride (0.252 mL, 3.48 mmol). The reaction was stirred, with warming from 0 °C to 25 °C for 16 h. The reaction was poured into saturated aqueous NH_4Cl (80 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (80 mL) and the combined organic phases were washed with saturated aqueous NaHCO_3 (80 mL), brine (80 mL), then dried (MgSO_4) and filtered. The solvent was removed *in vacuo* to yield **3.12** as a pale yellow oil (1.23 g, 100%) which was used without further purification.

An analytical sample was obtained by flash chromatography on silica (10% EtOAc – petroleum ether):

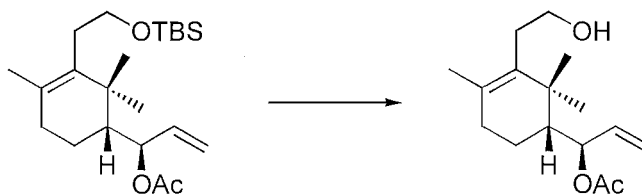
^1H nmr δ 0.06 (s, 6H), 0.83 (s, 3H), 0.90 (s, 9H), 1.08 (s, 3H), 1.39, (bd, 1H, $J = 11.8$ Hz), 1.63 (s, 3H), 1.92-1.96 (m, 2H), 2.03 (s, 3H), 2.29 (m, 2H), 3.48-3.59 (m, 2H), 5.07-5.15 (m, 2H), 5.57 (bd, 1H, $J = 4.8$ Hz), 5.72-5.83 (m, 1H).

^{13}C nmr δ -5.12, 18.43, 20.38, 21.24, 21.64, 26.05, 27.04, 32.74, 38.22, 48.70, 63.01, 73.14, 114.79, 129.30, 133.32, 137.29, 170.29.

FTIR (CDCl_3 , cm^{-1}) 1072.3, 1253.6, 1365.5, 1471.6, 1732.0, 2858.3, 2885.3, 2931.6, 2956.7.

HRMS (EI) calc. for $\text{C}_{22}\text{H}_{40}\text{O}_3\text{Si}$: 380.27467; found: 380.27370

(±)-(4*R)-((1*R**)-(Acetoxy)prop-2-enyl)-2-(2-hydroxyethyl)-1,3,3-trimethylcyclohex-1-ene 3.13**



Tetra-*n*-butylammonium fluoride (15.8 mL of 1.0 M in THF, 15.80 mmol) was added to a solution of **3.12** (1.23 g, 3.16 mmol) in THF (50 mL). The reaction was stirred at 25 °C for 2 h before being diluted with EtOAc – petroleum ether (100 mL, 1:1). The organic phase was washed with saturated aqueous NH₄Cl (100 mL), saturated NaHCO₃ (100 mL) and brine (100 mL). The organic phase was dried (MgSO₄), filtered, and the solvent removed *in vacuo* to yield pale yellow oil. Purification by flash chromatography on silica (50% EtOAc – petroleum ether) gave **3.13** as a clear oil (591 mg, 74% over two steps).

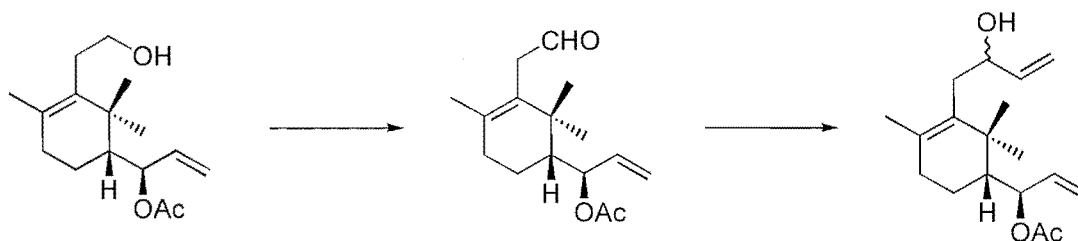
¹H nmr δ 0.06 (s, 6H), 0.83 (s, 3H), 0.90 (s, 9H), 1.08 (s, 3H), 1.39, (bd, 1H, *J* = 11.8 Hz), 1.63 (s, 3H), 1.92-1.96 (m, 2H), 2.03 (s, 3H), 2.29 (m, 2H), 3.48-3.59 (m, 2H), 5.07-5.15 (m, 2H), 5.57 (bd, 1H, *J* = 4.8 Hz), 5.72-5.83 (m, 1H).

¹³C nmr δ 18.37, 20.35, 21.24, 21.71, 27.07, 32.38, 32.71, 38.23, 48.65, 62.60, 73.01, 114.86, 129.78, 132.86, 137.21, 170.33.

FTIR (CDCl₃, cm⁻¹) 1022.2, 1245.9, 1373.2, 1732.0, 2943.2, 2974.0, 3500.6.

HRMS It was not possible to obtain an accurate mass under a number of conditions.

(±)-(4*R)-((1*R**)-(Acetoxy)prop-2-enyl)-2-((2*R**S*)-hydroxybut-3-enyl)-1,3,3-trimethylcyclohex-1-ene 3.14**



DMSO (0.240 mL, 3.38 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of oxalyl chloride (0.221 mL, 2.53 mmol) in CH_2Cl_2 (15 mL) at -78°C . After stirring at -78°C for 5 min the alcohol **3.13** (450 mg, 1.69 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction was stirred at -78°C for 1 h and triethylamine (0.942 mL, 6.76 mmol) was added and the reaction was allowed to warm to 25°C over 30 min. The reaction was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous NH_4Cl (40 mL), saturated NaHCO_3 (40 mL), and brine (40 mL). The organic phase was dried (MgSO_4), filtered, and the solvent removed *in vacuo* to yield a light yellow oil which was used directly.

The unstable intermediate aldehyde had the following spectroscopic characteristics:

^1H nmr δ 0.81 (s, 3H), 1.03 (s, 3H), 1.48 (d, 1H, $J = 11.7$ Hz), 1.56 (s, 3H), 1.58-1.88 (m, 2H), 1.93-2.09 (m, 2H), 2.03 (s, 3H), 3.09 (bs, 2H), 5.09-51.6 (m, 2H), 5.57 (bd, 1H, $J = 3.9$ Hz), 5.72-5.83 (m, 1H), 9.51 (t, 1H $J = 2.0, 4.3$ Hz).

^{13}C nmr δ 18.36, 20.34, 21.19 (two resonances), 26.70, 32.84, 43.86, 48.37, 72.93, 115.04, 128.72, 132.70, 137.00, 170.22, 200.83.

FTIR (CDCl_3 , cm^{-1}) 1022.2, 1245.9, 1373.2, 1672.2, 1735.8, 2937.4.

HRMS (EI) calc. for $\text{C}_{14}\text{H}_{20}\text{O}$ [$\text{M}^+ - \text{AcOH}$]: 204.15142; found: 204.15158.

The crude aldehyde was dissolved in THF (20 mL) and cooled to -78°C . Vinylmagnesium bromide (1.86 mL of 1.0 M in THF, 1.86 mmol) was added and the reaction stirred, with warming from -78°C to -20°C over a period of 1 h. The reaction was poured into a mixture of diethyl ether-saturated aqueous NH_4Cl (40 mL, 1:1) and the layers separated. The organic phase was dried (MgSO_4), filtered, and the solvent

removed *in vacuo* to give a light yellow viscous oil. Purification by flash chromatography on silica (12.5% EtOAc – petroleum ether gradient to 20% EtOAc – petroleum ether) gave the alcohol **3.14** (101 mg, 20% over two steps) as a *ca* 60:40 mixture of diastereoisomers. These diastereoisomers were separable, and a small sample of the less polar major diastereoisomer was characterized.

Less polar diastereoisomer:

^1H nmr δ 0.89 (s, 3H), 1.10 (s, 3H), 1.47 (dd, 1H, $J = 2.9, 11.2$ Hz), 1.60-1.73 (m, 2H), 1.69 (s, 3H), 2H), 1.96-2.10 (m, 2H), 2.03 (s, 3H), 2.26-2.33 (m, 2H), 4.27 (m, 1H), 5.07- 5.28 (m, 4H), 5.60 (bd, 1H, $J = 4.9$ Hz), 5.73 – 5.97 (m, 2H).

^{13}C nmr δ 18.34, 21.22, 21.36, 22.19, 27.40, 32.89, 36.21, 38.38, 48.65, 72.56, 72.99, 114.06, 114.89, 131.73, 133.33, 137.19, 141.11, 170.29.

FTIR (CDCl_3 , cm^{-1}) 1020.3, 1249.8, 1373.2, 1732.0, 2877.6, 2941.2, 3604.1.

HRMS (EI) calc. for $\text{C}_{16}\text{H}_{24}\text{O}$ [$\text{M}^+ - \text{AcOH}$]: 232.18272; found: 232.18226.

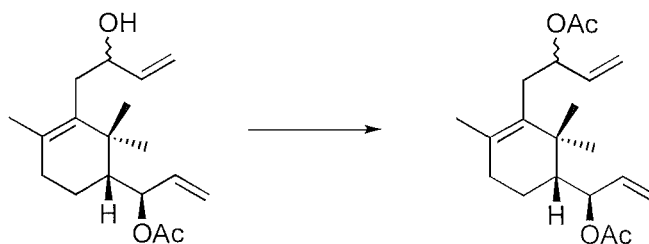
Mixture of diastereoisomers:

^1H nmr δ 0.89 (s, 3H, both isomers), 1.10 (s, 3H), 1.12 (s, 3H), 1.42 – 1.49 (m, 1H, both isomers), 1.62-1.71 (m, 2H, both isomers), 1.67 (s, 3H), 1.69 (s, 3H), 2H), 1.96 - 2.10 (m, 2H, both isomers), 2.03 (s, 3H), 2.04 (s, 3H), 2.25-2.40 (m, 2H, both isomers), 4.23 - 4.30 (m, 1H, both isomers), 5.05-5.28 (m, 4H, both isomers), 5.60 (m, 1H, both isomers), 5.73 – 5.97 (m, 2H, both isomers).

^{13}C nmr δ 18.34, 18.44, 21.22, 21.36, 21.48, 22.19, 22.69, 27.40, 27.97, 32.89, 36.21, 36.31, 38.38, 48.65, 48.67, 72.56, 72.81, 72.99, 73.30, 114.01, 114.06, 114.89, 137.19, 141.11, 170.29 (2 C).

FTIR (CDCl_3 , cm^{-1}) 1022.2, 1247.9, 1373.2, 1732.0, 2943.2, 2972.1, 3525.6, 3604.7.

(\pm)-2-((2*RS*)-(Acetoxy)but-3-enyl)-(4*R*^{*})-((1*R*^{*})-(acetoxy)prop-2-enyl)-1,3,3-trimethylcyclohex-1-ene 3.15



A mixture of the diastereoisomeric alcohols **3.14** (29 mg, 0.1 mmol) in CH_2Cl_2 (5 mL) at 0 °C was treated with DMAP (3 mg, 0.02 mmol) in CH_2Cl_2 (0.5 mL), Hünig's base

(0.021 mL, 0.12 mmol), and Ac₂O (0.008 mL, 0.11 mmol). The reaction was allowed to stir from 0 °C to 25 °C over 12 h before being diluted with CH₂Cl₂ (20 mL). The organic phase was washed with saturated aqueous NH₄Cl (20 mL), saturated aqueous NaHCO₃ (20 mL) and brine (20 mL). The organic phase was dried (MgSO₄), filtered, and the solvent removed *in vacuo* to yield a clear oil. Purification by flash chromatography on silica (10% EtOAc – petroleum ether) gave **3.15** as a *ca* 60:40 mixture of inseparable diastereoisomers as a clear oil (23 mg, 70%).

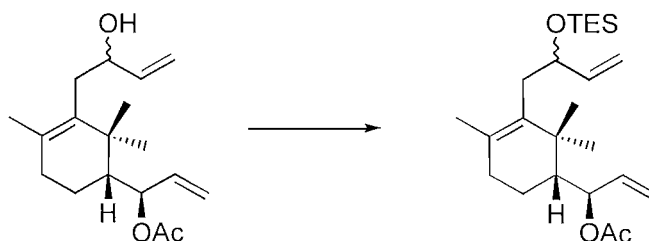
¹H nmr δ 0.83 (s, 3H), 0.84 (s, 3H), 1.09 (s, 3H), 1.10 (s, 3H), 1.37 – 1.47 (m, 1H, both diastereoisomers), 1.50 – 1.70 (m, 2H, both diastereoisomers), 1.66 (s, 3H, both diastereoisomers), 1.94 – 1.97 (m, 2H, both diastereoisomers), 2.00 (s, 3H), 2.02 (s, 3H), 2.03 (s, 3H), 2.04 (s, 3H), 2.23 – 2.32 (m, 1H, both diastereoisomers), 2.41 – 2.51 (m, 1H, both diastereoisomers), 5.07 – 5.25 (m, 4H, both diastereoisomers), 5.38 – 5.48 (m, 1H, both diastereoisomers), 5.55 – 5.58 (m, 1H, both diastereoisomers), 5.71 – 5.88 (m, 2H, both diastereoisomers).

¹³C nmr δ 18.28, 18.41, 21.14, 21.22, 21.28, 21.40, 21.95, 22.27, 26.99, 27.54, 32.92, 33.02, 33.28, 33.31, 38.33, 48.49, 48.88, 73.01, 73.10, 74.98, 75.10, 114.78, 114.86, 115.65, 130.75, 130.99, 132.62, 132.70, 136.63, 137.05, 137.24, 170.07, 170.26

FTIR (CDCl₃, cm⁻¹) 1022.7, 1097.4, 1247.4, 1367.9, 1456.2, 1645.2, 1714.6, 1716.5, 1793.7, 1816.8, 2252.7, 2942.2, 2979.8.

HRMS (EI) calc. for C₁₈H₂₆O₂ [M⁺ – AcOH]: 274.19328; found: 274.19300

(±)-(4*R)-((1*R**)-(Acetoxy)prop-2-enyl)-2-((2*RS*)-(triethylsilyloxy)but-3-enyl)-1,3,3-trimethylcyclohex-1-ene 3.16**



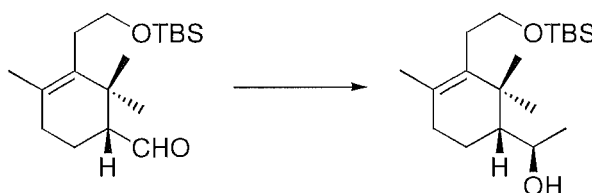
2,6-Lutidine (0.020 mL, 0.171 mmol), and TESOTf (0.020 mL, 0.089 mmol) were added sequentially to a solution of the diene alcohol (20 mg, 0.068 mmol) in CH₂Cl₂ (10 mL) cooled to -78 °C. After stirring, with warming from -78 °C to 0 °C, for 1 h TLC indicated there was no starting material left. The reaction was diluted with diethyl ether (30 mL) and washed with saturated aqueous NH₄Cl (2 x 50 mL), saturated

aqueous NaHCO₃, and brine (50 mL). The organic phase was then dried (MgSO₄), filtered, and the solvent removed *in vacuo* to yield a pale yellow oil.

Purification by flash chromatography (7.5% EtOAc – petroleum ether) gave a clear oil (7mg, 25%). ¹H nmr analysis indicated that this oil was *ca* 90% pure. The main contaminants were unidentified silyl impurities.

¹H nmr δ 0.52 (m, 6H), 0.80-1.00 (m, 12H), 1.07 (m, 3H, major diastereoisomer), 1.08 (s, 3H, minor diastereoisomer), 1.40 (m, 1H), 1.65 (s, 3H), 1.50-1.70 (m, 2H), 1.95 (m, 2H), 2.04 (s, 3H), 2.10-2.40 (m, 2H), 4.30 (m, 1H), 4.90-5.15 (m, 4H), 5.58 (m, 1H), 5.70-5.90 (m, 1H).

(±)-2-((2-(*tert*-Butyldimethylsilyloxy)ethyl)-(4*R)-((1*R**)-(hydroxyethyl)-1,3,3-trimethylcyclohex-1-ene 3.17**



The procedure used below for the addition of ethynylmagnesium bromide was used here for the reaction of methylmagnesium iodide (0.4 mL of 1.0 M in THF, 40 mmol) with aldehyde **2.29** (103 mg, 0.33 mmol). Purification by flash chromatography (10% EtOAc – petroleum ether) gave **3.17** (64 mg, 59%).

Only one diastereoisomer could be detected by ¹H NMR analysis.

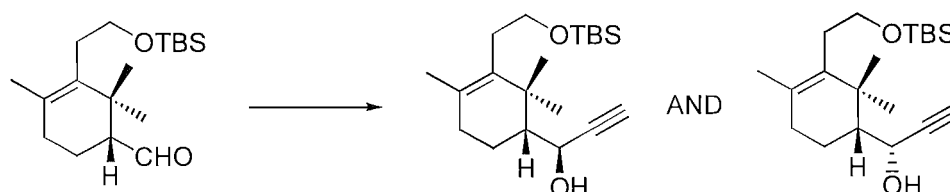
¹H nmr δ 0.06 (s, 6H), 0.90 (s, 12H), 1.02 (s, 3H), 1.16 (m, 1H) 1.20 (d, 3H, *J* = 6.8 Hz), 1.42-1.55 (m, 2H), 1.64 (s, 3H), 2.00 (m, 2H), 2.30 (m, 2H), 3.55 (m, 2H), 4.18 (q, 1H, *J* = 6.3 Hz).

¹³C nmr δ -5.12, 17.58, 20.35, 22.51, 23.43, 26.05, 27.45, 32.52, 32.65, 38.27, 50.71, 63.01, 66.65, 129.67, 142.70.

FTIR (CDCl₃, cm⁻¹) 1006.8, 1024.1, 1091.6, 1136.0, 1255.6, 1361.7, 1463.9, 1471.6, 2858.3, 2885.3, 2929.7, 2958.6, 3421.5.

HRMS (EI) calc. for C₁₉H₃₈O₂Si: 326.26411; found: 326.26377.

(±)-2-((2-(*tert*-Butyldimethylsilyloxy)ethyl)-(4*R**)-((1*R**)-(hydroxypropynyl)-1,3,3-trimethylcyclohex-1-ene and
 (±)-2-((2-(*tert*-Butyldimethylsilyloxy)ethyl)-(4*R**)-((1*S**)-(hydroxypropynyl)-1,3,3-trimethylcyclohex-1-ene **3.18**



Ethynylmagnesium bromide (0.8 mL of 0.5 M in THF, 0.40 mmol) was added to a solution of the aldehyde **2.29** (103mg, 0.33 mmol) in THF (10 mL) at -78 °C. The reaction was allowed to stir from -78 °C to -20 °C over a period of 1 h. The reaction was poured into diethyl ether-saturated aqueous NH₄Cl (1:1, 10mL) and the layers separated. The aqueous layer was extracted with diethyl ether (2 x 10 mL) and the combined organic phases were washed with brine (20 mL), dried (MgSO₄), filtered, and the solvent removed *in vacuo* to yield a pale yellow oil. Purification by flash chromatography on silica (10% EtOAc – petroleum ether) gave **3.18** as a clear oil (62 mg, 6:1 mixture of diastereoisomers, 56% over 4 steps).

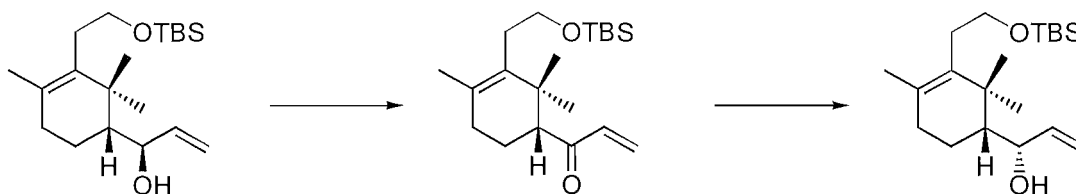
¹H nmr (mixture of diastereoisomers) δ 0.06 (s, 6H, both diastereoisomers), 0.90 (s, 9H, both diastereoisomers), 0.97 (s, 3H, minor diastereoisomer), 1.02 (s, 3H, major diastereoisomer), 1.09 (s, 3H, major diastereoisomer), 1.12 (s, 3H, minor diastereoisomer), 1.55 (t, 1H, *J* = 2.4 Hz, minor diastereoisomer), 1.58 (t, 1H, *J* = 2.4 Hz, major diastereoisomer), 1.64 (s, 3H, both diastereoisomers), 1.70-1.93 (m, 2H, both diastereoisomers), 2.03 (m, 2H, both diastereoisomers), 2.30 (m, 2H, both diastereoisomers), 2.44 (d, 1H, *J* = 2.4 Hz, major diastereoisomer), 2.28 (d, 1H, *J* = 2.0 Hz, minor diastereoisomer), 3.55 (m, 2H, both diastereoisomers), 4.57 (bs, 1H, minor diastereoisomer), 4.71 (bs, 1H, major diastereoisomer).

¹³C nmr (mixture of diastereoisomers) δ -5.13, 18.40, 18.80, 20.35, 20.53, 22.43, 23.00, 26.04, 27.09, 27.69, 32.11, 32.53, 37.91, 51.08, 51.19, 62.73, 62.94, 63.47, 72.33, 74.64, 76.58, 85.90, 129.38, 129.60, 133.42.

FTIR (CDCl₃, cm⁻¹) 1068.5, 1255.6, 1471.6, 2929.7, 2956.7, 3012.6, 3305.8.

HRMS (EI) calc. for C₁₆H₂₇O₂Si [M⁺ - C₄H₉]; 279.17803; found: 279.17843.

(±)-2-((2-*tert*-Butyldimethylsilyloxy)ethyl)-(4*R)-((1*S**)-hydroxyprop-2-enyl)-1,3,3-trimethylcyclohex-1-ene **3.19****



DMSO (0.142 mL, 2.0 mmol) dissolved in CH_2Cl_2 (5 mL) was added dropwise to oxalyl chloride (0.131 mL, 1.5 mmol) in CH_2Cl_2 (10 mL) at -78°C . After stirring for 5 min, alcohol **3.13** (339 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added and the reaction was stirred at -78°C for 1 h. Triethylamine (0.558 mL, 4 mmol) was then added and the reaction was allowed to warm from -78°C to 25°C over a period of 30 min. The reaction was diluted with CH_2Cl_2 (50 mL) and poured into saturated aqueous NH_4Cl (100 mL). The layers were separated and the organic phase was washed with saturated aqueous NH_4Cl (100 mL), saturated aqueous NaHCO_3 (100 mL), and brine (100 mL), then dried (MgSO_4), filtered, and the solvent removed *in vacuo* to yield a clear film.

The unstable crude enone had the following spectroscopic characteristics:

^1H nmr δ 0.07 (s, 6H), 0.90 (s, 9H), 0.98 (s, 3H), 1.10 (s, 3H), 1.78-2.03 (m, 4H), 1.65 (s, 3H), 2.20-2.40 (m, 2H), 2.76 (dd, 1H, $J = 2.9, 11.2$ Hz), 3.57 (m, 2H), 5.68 (dd, 1H, $J = 1.0, 10.2$ Hz), 6.22 (dd, 1H, $J = 1.5, 11.6$ Hz), 6.48 (dd, 1H, $J = 10.3, 17.6$ Hz).
HRMS (EI) calc. for $\text{C}_{16}\text{H}_{27}\text{O}_2\text{Si}$ [$\text{M}^+ - \text{C}_4\text{H}_9$]: 279.17803; found: 279.17873.

DIBAL-H (0.150 mL of 1.0 M in hexanes, 0.15 mmol) was added to a -78°C solution of the enone (34 mg, 0.1 mmol) in CH_2Cl_2 (2 mL). After stirring for 10 min at -78°C , the reaction was quenched by the addition of 10% aqueous HCl (5 mL). After dilution with CH_2Cl_2 (10 mL), the organic phase was separated and washed with 10% aqueous HCl (2 x 10 mL), saturated aqueous NaHCO_3 (10 mL) and brine (10 mL), then dried (MgSO_4), filtered, and the solvent removed *in vacuo* to yield a clear oil (32 mg). ^1H

NMR analysis showed a 3:1 mixture of the diastereoisomeric alcohols plus also ca. 25% of the product derived from 1,4 conjugate addition of the hydride. Purification by flash chromatography on silica (10% EtOAc – petroleum ether) gave **3.19** as a clear oil (16 mg, 48%).

^1H nmr δ 0.07 (s, 6H), 0.90 (s, 9H), 0.93 (s, 3H), 1.17 (s, 3H), 1.23-1.35 (m, 1H), 1.49-1.56 (m, 2H), 1.63 (s, 3H), 1.66-1.70 (m, 1H), 1.96 (m, 2H), 2.29 (m, 2H), 3.55 (m, 2H), 4.28 (m, 1H, $J = 2.9$ Hz), 5.14 (m, 1H), 5.23 (m, 1H), 5.90-6.01 (m, 1H).

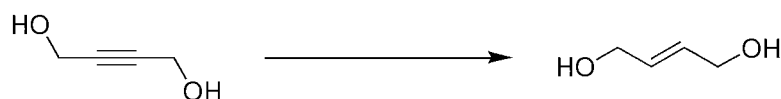
^{13}C nmr δ -5.11, 18.41, 20.38, 20.88, 22.48, 26.06, 27.63, 32.41, 32.63, 37.93, 50.87, 63.08, 74.34, 115.97, 129.13, 133.86, 140.46.

FTIR (CDCl_3 , cm^{-1}) 1068.4, 1089.7, 1255.6, 1471.6, 2858.3, 2885.3, 2929.7, 2956.7, 3600.9.

HRMS (EI) calc. for $\text{C}_{20}\text{H}_{36}\text{OSi}$ [$\text{M}^+ - \text{H}_2\text{O}$]: 320.25355; found: 320.25304.

7.5 Experiments Described in Chapter 4[†]

(*E*)-But-2-ene-1,4-diol¹⁶⁰



But-2-yne-1,4-diol (20.0 g, 232 mmol) in THF (20 mL) was added dropwise from a dropping funnel over a period of ca. 60 min to a suspension of lithium aluminium hydride (19.4 g, 510 mmol) in THF (380 mL) at 0 °C. The dropping funnel was washed with a further 20 mL of THF. The reaction was carefully allowed to warm to 25 °C over a period of ca. 30 min before being heated at reflux for 18 h. The mixture was cooled to room temperature and Celite[®] (5g) was added. The reaction was carefully quenched with saturated ammonium sulfate solution (*ca* 25 mL). The white salts were removed by filtration and the filter cake was washed with EtOAc. The combined organic phases were dried (MgSO₄) and the solvent removed *in vacuo* to yield a pale yellow oil (16.3 g, 80%).

This material was used without further purification.

¹H nmr δ 4.17 (bs, 4H), 5.88 (bs, 2H).

[†] A number of compounds in this chapter are racemic mixtures of diastereoisomers. For simplicity they are drawn and named as the major racemic diastereoisomer.

(±)-(4*R)-Ethenyl-(3*RS*)-methyl-tetrahydrofuran-2-one 4.4**¹⁶¹

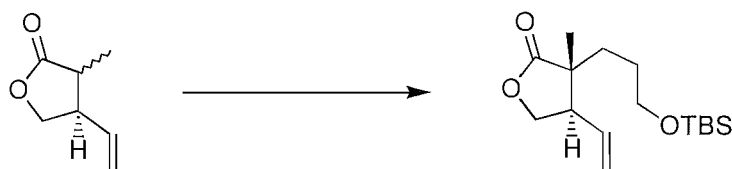
A mixture of (*E*)-but-2-ene-1,4-diol (2.00 g, 23 mmol), triethyl orthopropionate (8.00 g, 46 mmol) and hydroquinone (0.2 g) was heated at 150 °C for 16 h with continuous removal of ethanol by a downwards distillation apparatus. Fractional distillation of the reaction mixture gave the product **4.4** as a 1.4:1.0 mixture of diastereoisomers (1.76 g, 70%).

Bp 52-56 °C (3 mmHg)

¹H nmr (major diastereoisomer) δ 1.22 (d, 3H, *J* = 7.3 Hz), 2.28-2.39 (m, 1H), 2.68-2.81 (m, 1H), 3.88 (dd, 1H, *J* = 8.8, 10.3 Hz), 4.35 (dd, 1H, *J* = 8.6, 9.6 Hz), 5.17-5.26 (m, 2H), 5.62-5.77 (m, 1H).

HRGCMS (EI) calc. for C₇H₁₀O₂: 126.06808; found: 126.0679.

¹H nmr (minor diastereoisomer) δ 1.14 (d, 3H, *J* = 7.8 Hz), 2.68-2.81 (m, 1H), 3.09-3.19 (m, 1H), 4.14 (dd, 1H, *J* = 3.9, 9.3 Hz), 4.31-4.38 (m, 1H), 5.17-5.26 (m, 2H), 5.62-5.77 (m, 1H).

(±)-(3*R)-(3-*tert*-Butyldimethylsilyloxypropyl)-(4*R**)-ethenyl-3-methyltetrahydrofuran-2-one 4.5**

The butenolide **4.4** (1.26 g, 10 mmol) in THF (5 mL) was added dropwise over ca. 2 min to a solution of LDA (5.50 mL of 2.0 M in THF/PhEt/heptane, 11 mmol) in THF (30 mL) at -78 °C. The reaction was stirred for 1 h from -78 °C to -20 °C and was then cooled back to -78 °C. DMPU (2.42 mL, 20 mmol) was added followed by 3-bromo-1-*tert*-butyldimethylsilyloxypropane (3.04 g, 12 mmol) in THF (2 mL). The reaction was

stirred, with warming from -78 °C to 25 °C over a period of 14 h before being quenched with saturated aqueous NH₄Cl (20mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with saturated aqueous NaHCO₃ (40 mL), brine (40 mL), dried (MgSO₄), filtered and the solvent removed *in vacuo* to yield a clear yellow oil. Purification by flash chromatography (17% EtOAc – petroleum ether) gave **4.5** as *ca* 3:1 mixture of diastereoisomers a clear oil (4.92 g, 83%). It was also possible to purify this compound by distillation.

Bp 86 °C @ 2mmHg.

¹H nmr (mixture of diastereoisomers, major diastereoisomer) δ 0.03 (s, 6H), 0.88 (s, 9H), 1.09 (s, 3H), 1.58-1.69 (m, 4H), 3.04 (m, 1H), 3.54-3.66 (m, 2H), 3.96-4.08 (m, 1H), 4.29-4.35 (m 1H), 5.14-5.23 (m, 2H), 5.63-5.75 (m, 1H).

¹³C nmr (mixture of diastereoisomers, major diastereoisomer) δ -5.33, 18.00, 21.19, 25.91, 27.39, 32.69, 45.25, 47.40, 63.04, 68.44, 119.55, 132.67, 181.13.

FTIR (CDCl₃, cm⁻¹) 1097.9, 1256.5, 1383.3, 1462.9, 1472.5, 1775.9, 2929.7, 2954.3.

HRMS (EI) calc. for C₁₅H₂₇O₃Si: 283.17295; found: 283.17332.

Selected data for the minor diastereoisomer:

¹H nmr (selected resonances) δ 0.02 (s, 6H), 0.87 (s, 9H), 1.21 (s, 3H), 1.45-1.56 (m, 4H), 2.89 (m, 1H).

¹³C nmr δ 18.24, 18.27, 25.88, 27.24, 28.95, 45.08, 51.59, 62.93, 68.59, 119.48, 132.19, 180.66.

(±)-(4*R)-Ethenyl-(3*R**)-(3-hydroxypropyl)-3-methyltetrahydrofuran-2-one **4.6****



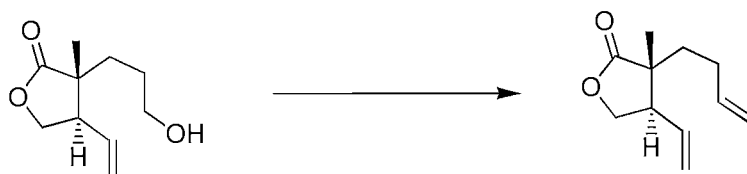
Tetra-*n*-butylammonium fluoride (8.00 mL of 1.0 M in THF, 8 mmol) was added to a solution of the silyl ether **4.5** (1.20 g, 4 mmol) in THF (40 mL) at 25°C. After 1 h, TLC showed no starting material was present. The reaction was diluted with EtOAc (100

mL) and washed with saturated aqueous NH_4Cl (2 x 100 mL), then dried (Mg SO_4), filtered and the solvent removed *in vacuo* to yield a clear yellow oil. Purification by flash chromatography (66% EtOAc – petroleum ether) gave **4.6** as a clear oil (405 mg, 55%) contaminated with *ca* 10% of silyl impurities.

^1H nmr (mixture of diastereoisomers, major diastereoisomer) δ 1.12 (s, 3H), 1.40-2.00 (m, 4H), 3.05 (m, 1H), 3.70 (m, 2H), 4.03 (m, 1H), 4.35 (m, 1H), 5.17-5.26 (m, 2H), 5.64-5.80 (m, 1H).

HRMS (EI) calc. for $\text{C}_9\text{H}_{13}\text{O}_3$ [$\text{M}^+ - \text{CH}_3$]: 169.08647; found: 169.08628.

(\pm)-(3*R)-(But-3-enyl)-(4*R**)-ethenyl-3-methyltetrahydrofuran-2-one 4.7**



DMSO (0.191 mL, 2.70 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a solution of oxalyl chloride (0.178 mL, 2.03 mmol) in CH_2Cl_2 (5 mL) at -78°C . After stirring the clear solution for 5 min at -78°C , a solution of the alcohol **4.6** (250 mg, 1.35 mmol) in CH_2Cl_2 (1 mL) was added and the reaction was stirred at -78°C for 30 min. Triethylamine (0.920 mL, 6.75 mmol) was then added dropwise and after stirring for 5 min at -78°C , the reaction was allowed to warm from -78°C to 25°C over a period of 30 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL). The combined organic phases were washed with saturated aqueous NaHCO_3 (50 mL), saturated aqueous NH_4Cl (50 mL) and brine (50 mL), then dried (MgSO_4), filtered and the solvent removed *in vacuo* to quantitatively yield the aldehyde as a light brown oil (261 mg). This oil was used without further purification.

n-Butyllithium (0.93 mL of 1.6 M in hexanes, 1.49 mmol) was added dropwise to a suspension of methyltriphenylphosphonium bromide (579 mg, 1.62 mmol) in THF (8 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h resulting in a clear pale yellow solution. This solution was cooled to -78 °C and the crude aldehyde in THF (2 mL) was added dropwise. The reaction was allowed to stir from -78 °C to 25 °C over a period of 6 h before being poured into saturated aqueous NH₄Cl (20 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with brine (50 mL), dried (MgSO₄), filtered and the solvent removed *in vacuo* to give a pale yellow oil. Purification by flash chromatography on silica (17% EtOAc- petroleum ether) gave **4.7** as a clear oil (133 mg, 55%) contaminated with *ca* 10% of silyl impurities.

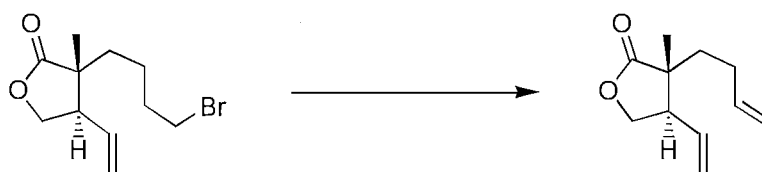
Full data are presented below.

Dichlorobis(triphenylphosphine)nickel (II) dichloride

NiCl₂·6H₂O, (11.90g, 50 mmol) and triphenylphosphine (26.20g, 100 mmol) were heated at reflux in EtOH (200 mL). After 3 h the reaction was filtered whilst hot and the collected solid was then washed with boiling EtOH (3 x 100 mL). The dark green complex obtained was dried under vacuum to remove residual EtOH. Yield 24.1g (74%). The complex was stored under argon. In the author's experience the use of this complex for the elimination reaction below is unreliable after it has been stored for long periods .

(±)-(3*R)-(But-3-enyl)-(4*R**)-ethenyl-3-methyltetrahydrofuran-2-one 4.7**

Alternative preparation by bromide elimination



Freshly prepared dichlorobis(triphenylphosphine)nickel (II) (3.43 g, 5.25 mmol) and triphenylphosphine (2.75 g, 10.50 mmol) were suspended in THF (150 mL). The suspension was degassed by 3 freeze-pump-thaw cycles and was then cooled to 0 °C. *n*-Butyllithium (6.56 mL of 1.6 M in hexanes, 10.50 mmol) was added. After stirring for 10 min, the bromide **4.11** (1.30 g, 5 mmol) and DBU (1.57 mL, 10.50 mmol) in THF (10 mL) were added to the homogenous blood red solution. The reaction was stirred for 1 h at 0 °C and then at 25 °C for 2.5 h. At this point TLC showed clean transformation to a slightly higher running spot. The blood red solution was exposed to the atmosphere for 30 min and then saturated aqueous NH₄Cl (100 mL) was added. After stirring at 25 °C for 10 min the layers were separated and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine (100 mL), dried (MgSO₄), filtered and the solvent removed *in vacuo* to yield a white solid. This solid was suspended in 17% EtOAc – petroleum ether and stirred for 2 h. The solids were filtered and the filtrate concentrated to give a light yellow oil. Purification by flash chromatography on silica (17% EtOAc – petroleum ether) gave **4.7** (512 mg, 57%).

¹H nmr δ 1.12 (s, 3H), 1.57-1.78 (m, 2H), 2.00-2.34 (m, 2H), 3.06 (m, 1H), 4.00 (m, 1H), 4.30 (m, 1H), 4.95-5.26 (m, 4H), 5.64-5.86 (m, 2H).

¹³C nmr (mixture of diastereoisomers, major diastereoisomer) δ 17.95, 28.30, 35.42, 45.34, 47.31, 68.39, 115.04, 119.68, 132.54, 137.74, 181.00.

FTIR (CDCl₃, cm⁻¹) 1022.2, 1315.4, 1535.2, 1766.7, 2981.7.

HRMS It was not possible to obtain an accurate mass under a number of conditions.

Selected data for the minor diastereoisomer:

¹³C nmr (mixture of diastereoisomers, major diastereoisomer) δ 21.04, 28.14, 31.72, 45.17, 51.59, 115.04, 119.67, 132.04, 137.65, 180.40.

(±)-(3a*R,7a*R**)-3a,4,5,7a-Tetrahydro-1(3*H*)-isobenzofuranone 4.8**

The diene **4.7** (360 mg, 2 mmol) was dissolved in freshly distilled PhH (200 mL) and the solution was degassed by three freeze-pump-thaw cycles. This solution was then heated to reflux and dichlorobis(tricyclohexylphosphine)benzylidene ruthenium (IV) (Grubbs' catalyst) (329 mg, 0.4 mmol, 20 mol%) in PhH (1 mL, degassed as above) was added. The purple color imparted by the benzylidene catalyst changed almost immediately to give a yellow-orange solution. After 4.5 h, the reaction was cooled to 25 °C and the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica (20% EtOAc – petroleum ether) to give **4.8** as a light yellow oily solid (208 mg, 68%). ¹H nmr analysis showed the ratio of diastereoisomers to be 2.2:1 (*trans*:*cis*).

¹H nmr (mixture of diastereoisomers, major diastereoisomer) δ 1.10 (s, 3H), 1.70-1.97 (m, 2H), 2.21-2.36 (m, 2H), 2.95 (m, 1H), 4.04 (dd, 1H, *J* = 8.2, 12.2 Hz), 4.36 (t, 1H, *J* = 7.8), 5.65-5.75 (m, 2H).

¹³C nmr (mixture of diastereoisomers, major diastereoisomer) δ 13.41, 23.42, 28.81, 40.50, 43.83, 68.81, 120.95, 129.45, 180.26.

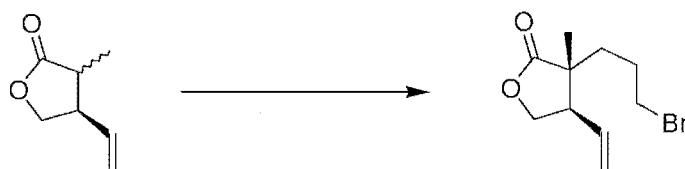
FTIR (CDCl₃, cm⁻¹) 1058.8, 1195.8, 1377.1, 1463.9, 1789.8, 2854.5.

HRMS (EI) calc. for C₉H₁₂O₂: 152.08373; found: 152.08421.

Selected nmr data for minor diastereoisomer:

¹H nmr δ 1.25 (s, 3H), 1.49-1.58 (m, 1H), 1.85 (m, 1H), 2.05 (m, 2H), 2.65 (m, 1H), 3.91 (dd, 1H, *J* = 4.4, 8.8 Hz), 4.44 (dd, 1H, *J* = 7.3, 9.2), 5.55-5.64 (m, 1H), 5.86-5.92 (m, 1H).

¹³C nmr (mixture of diastereoisomers, major diastereoisomer) δ 21.22, 21.91, 27.33, 40.80, 42.24, 70.78, 124.67, 129.45, 181.27.

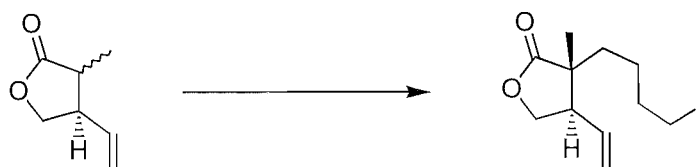
(±)-(3*R)-(3-Bromopropyl)-(4*R**)-ethenyl-3-methyltetrahydrofuran-2-one 4.9**

The butenolide **4.4** (252 mg, 2 mmol) in THF (1 mL) was added dropwise over *ca* 2 min to a solution of LHMDs (2.20 mL of 1.0 M in THF, 2.2 mmol) in THF (10 mL) at -78 °C. The reaction was stirred for 1 h from -78 °C to -20 °C and was then cooled back to -78 °C. DMPU (0.484 mL, 2 mmol) was added followed by 1,4-dibromopropane (0.304 mL, 3 mmol). The reaction was stirred, with warming from -78 °C to 25 °C over a period of 14 h before being quenched with saturated aqueous NH₄Cl (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with saturated aqueous NaHCO₃ (50 mL), brine (50 mL), dried (MgSO₄), filtered and the solvent removed *in vacuo* to yield a clear yellow oil. Purification by flash chromatography (17% EtOAc – petroleum ether) gave **4.9** as a clear oil (334 mg, 71%). ¹H nmr analysis showed the ratio of diastereoisomers to be 3:1 (*trans*:*cis*).

¹H nmr (mixture of diastereoisomers, major diastereoisomer) δ 1.12 (s, 3H), 1.70 (m, 2H), 1.83-2.09 (m, 2H), 2.99 (m, 1H), 3.31-3.46 (m, 2H), 4.04 (m, 1H), 4.34 (m, 1H), 5.19-5.29 (m, 2H), 5.63-5.75 (m, 1H).

FTIR (CDCl₃, cm⁻¹) 1017.1, 1219.9, 1253.6, 1383.1, 1767.4, 2941.6, 2966.0.

HRMS (EI) calc. for C₉H₁₂O₂: 152.08373; found: 152.08421.

(±)-(4*R)-Ethenyl-(3*R**)-(4-Iodobutyl)-3-methyltetrahydrofuran-2-one 4.10**

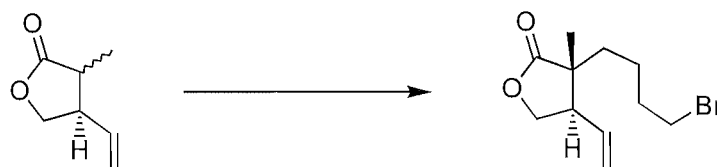
The butenolide **4.4** (1.26 g, 10 mmol) in THF (5 mL) was added dropwise over *ca* 2 min to a solution of LHMDs (11.00 mL of 1.0 M in THF, 11 mmol) in THF (30 mL) at -78 °C. The reaction was stirred for 1 h from -78 °C to -20 °C and was then cooled back to -78 °C. DMPU (2.42 mL, 20 mmol) was added followed by 1,4-diiodobutane (4.65 g, 15 mmol). The reaction was stirred, with warming from -78 °C to 25 °C over a period of 14 h before being quenched with saturated aqueous NH₄Cl (50 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with saturated aqueous NaHCO₃ (100 mL), brine (100 mL), dried (MgSO₄), filtered and the solvent removed *in vacuo* to yield a clear yellow oil. Purification by flash chromatography (17% EtOAc – petroleum ether) gave **4.10** as a clear oil (1.88 g, 61%). ¹H nmr analysis showed the ratio of diastereoisomers to be 7:5 (*trans*:*cis*).

¹H nmr (mixture of diastereoisomers) δ 1.10 (s, 3H, major diastereoisomer), 1.23 (s, 3H, minor diastereoisomer), 1.31-1.62 (m, 8H, both diastereoisomers), 1.74-1.87 (m, 4H, both diastereoisomers), 2.89 (m, 1H, minor diastereoisomer), 3.05 (m, 1H, major diastereoisomer), 3.12-3.22 (m, 4H, both diastereoisomers), 3.97-4.09 (m, 2H, both diastereoisomers), 4.31-4.37 (m, 2H, both diastereoisomers), 5.18-5.26 (m, 4H, both diastereoisomers), 5.64-5.82 (m, 2H, both diastereoisomers).

¹³C nmr (mixture of diastereoisomers) δ 5.98, 6.44, 17.92, 21.25, 24.87, 31.56, 33.38, 33.77, 35.01, 45.25, 45.43, 47.27, 51.33, 68.38, 68.66, 76.57, 119.64, 119.89, 132.10, 132.37, 180.47, 181.01.

FTIR (CDCl₃, cm⁻¹) 1234.4, 1284.5, 1415.7, 1697.2, 2877.6.

HRMS (EI) calc. for C₁₁H₁₈O₂I [MH⁺, self CI]: 309.03494; found: 309.03516.

(±)-(3*R)-(4-Bromobutyl)-(4*R**)-ethenyl-3-methyltetrahydrofuran-2-one 4.11**

The butenolide **4.4** (1.26 g, 10 mmol) in THF (10 mL) was added dropwise over *ca* 2 min to a solution of LHMDS (11.00 mL of 1.0 M in THF, 11 mmol) in THF (10 mL) at -78 °C. The reaction was stirred for 1 h from -78 °C to -20 °C and was then cooled back to -78 °C. DMPU (2.42 mL, 20 mmol) was added and the reaction was then cooled to -95 °C and stirred for 20 min. 1,4-Dibromobutane (1.79 mL, 15 mmol) was then added and the reaction was stirred at -95 °C for 30 min and then from -78 °C to 25 °C over a period of 14 h before being quenched with saturated aqueous NH₄Cl (20 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with saturated aqueous NaHCO₃ (100 mL), brine (100 mL), dried (MgSO₄), filtered and the solvent removed *in vacuo* to yield a clear yellow oil. Purification by flash chromatography (17% EtOAc – petroleum ether) gave **4.11** as a clear oil (1.89 g, 76%). ¹H nmr analysis showed the ratio of diastereoisomers to be 3:1 (*trans*:*cis*).

¹H nmr (mixture of diastereoisomers, major diastereoisomer) δ 1.09 (s, 3H), 1.49-1.63 (m, 4H), 1.78-1.88 (m, 2H), 3.03 (m, 1H), 3.34-3.43 (m, 2H), 3.99 (m, 1H), 4.34 (m, 1H), 5.16-5.25 (m, 2H), 5.63-5.80 (m, 1H).

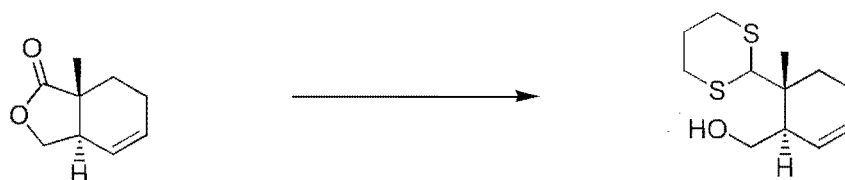
¹³C nmr (mixture of diastereoisomers, major diastereoisomer) δ 17.76, 22.38, 31.58, 32.85, 35.08, 47.06, 51.14, 68.21, 119.63, 132.26, 180.82.

FTIR (CDCl₃, cm⁻¹) 1016.9, 1219.9, 1253.6, 1382.9, 1457.1, 1768.6, 2941.7, 2966.3.

HRMS (EI) calc for C₁₁H₁₇O₂⁸¹Br: 262.03861; found: 262.03927.

Selected ¹H nmr resonances for the minor diastereoisomer:

¹H nmr δ 1.22 (s, 3H), 2.88 (m, 1H).

(±)-2-((2*R)-Hydroxymethyl-(1*R**)-methylcyclohex-3-enyl)-1,3-dithiane 4.12**

DIBAL-H (0.66 mL of 1.0 M in toluene, 0.66 mmol) was added to a solution of the lactone (100 mg, 0.66 mmol) in dry PhMe (5 mL) at -78 °C. The reaction was stirred at this temperature for 1.5 h and then quenched by the careful addition of 10% aqueous H₂SO₄ (5 mL). After warming to room temperature the layers were separated and the aqueous phase extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with saturated aqueous NaHCO₃ (20 mL), brine (20 mL) and then dried (MgSO₄), filtered and the solvent removed *in vacuo* to give the crude aldehyde which was used without purification.

¹H nmr (diagnostic resonances) δ 9.46 (s, 1H).

The crude aldehyde obtained above was dissolved in dry CH₂Cl₂ (5 mL), cooled to 0 °C, and treated with propane-1,3-dithiol (0.133 mL, 1.32 mmol) and BF₃·OEt₂ (0.251 mL, 1.98 mmol). The reaction was stirred at 0 °C for 3 h and was then poured into saturated aqueous NaHCO₃ (20 mL). The mixture was extracted with EtOAc (2 x 20 mL) and the combined organic phases were washed with brine (50 mL), dried (MgSO₄), and the solvent removed *in vacuo* to give a pale brown oil. Purification by flash chromatography (20% EtOAc – petroleum ether) gave firstly returned starting material (18 mg), and then **4.12** as a colorless oil (89 mg, 68% based on returned starting material).

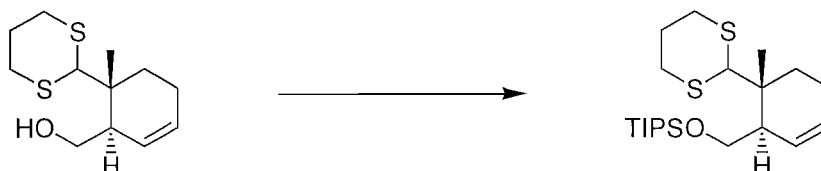
¹H nmr δ 1.10 (s, 3H), 1.64-2.12 (m, 6H), 2.81 (m, 1H), 2.88 (m, 4H), 3.57 (1H, dd, *J* = 5.9, 10.7 Hz), 3.74 (1H, dd, *J* = 5.4, 10.7), 4.39 (s, 1H), 5.52-5.57 (m, 1H), 5.79-5.85 (m, 1H).

^{13}C nmr δ 19.91, 22.29, 26.44, 29.92, 31.51, 31.62, 39.08, 42.63, 59.20, 63.57, 126.44, 128.35.

FTIR (CDCl_3 , cm^{-1}) 1095.5, 1380.9, 1461.9, 2902.7, 2935.5, 3301.0

HRMS (EI) calc for $\text{C}_{12}\text{H}_{20}\text{OS}_2$: 244.09556; found: 244.09527.

(\pm)-2-((1*R)-methyl-(2*R**)-(triisopropylsilyloxy)methylcyclohex-3-enyl)-1,3-dithiane 4.13**



Triisopropyl triflate (0.063 mL, 0.23 mmol) was added to a solution of the dithiane (52 mg, 0.22 mmol), and 2,6-lutidine (0.064 mL, 0.55 mmol) in CH_2Cl_2 (5 mL) at $-78\text{ }^\circ\text{C}$. The reaction was allowed to warm, with stirring, over a period of 16 h. The reaction was then poured into H_2O – diethyl ether (1:1, 20 mL) and the layers were separated. The organic phase was washed with saturated aqueous NH_4Cl (20 mL), saturated aqueous NaHCO_3 (20 mL) and brine (20 mL), then dried (MgSO_4), filtered, and the solvent removed *in vacuo* to yield a clear oil. Purification by flash chromatography (14% EtOAc – petroleum ether) gave **4.13** as a clear oil (90 mg, 100%).

^1H nmr δ 0.99-1.13 (m, 24H), 1.69-2.13 (m, 6H), 2.80-2.91 (m, 5H), 3.58 (1H, dd, $J = 6.8, 9.8$ Hz), 3.78 (1H, dd, $J = 6.4, 9.8$ Hz), 4.47 (s, 1H), 5.53-5.59 (m, 1H), 5.69-5.76 (m, 1H).

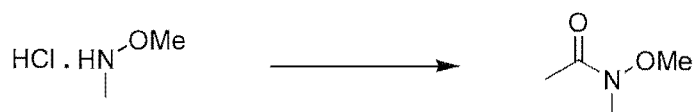
^{13}C nmr δ 11.96, 13.37, 18.06, 19.77, 22.27, 26.56, 29.96, 31.46, 31.64, 38.98, 42.35, 59.31, 64.23, 126.74, 127.50.

FTIR (CDCl_3 , cm^{-1}) 1234.4, 1419.5, 2970.2.

HRMS (EI) calc. for $\text{C}_{18}\text{H}_{33}\text{OS}_2\text{Si}$ [$\text{M}^+ - \text{C}_3\text{H}_7$]: 357.17422; found 357.17461.

7.6 Experiments Described in Chapter 5

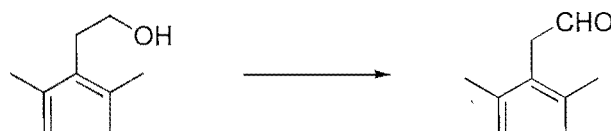
N-Methoxy-*N*-methylacetamide **5.1**



Acetyl chloride (2.00 mL, 28.19 mmol) was added dropwise to a solution of *N,O*-dimethylhydroxylamine hydrochloride (2.50 g, 25.63 mmol) and triethylamine (7.86 mL, 56.39 mmol) in CH₂Cl₂ (50 mL) at 0 °C. The reaction was allowed to stir from 0 °C to 25 °C over a period of 16 h, before being quenched with saturated aqueous NH₄Cl (50 mL). The layers were separated, and the aqueous phase was extracted with CH₂Cl₂ (50 mL). The combined organic phases were washed with saturated aqueous NH₄Cl (50 mL), saturated aqueous NaHCO₃ (50 mL), and brine (50 mL), then dried (MgSO₄), filtered, and the solvent removed *in vacuo* to give a pale yellow oil. Purification by distillation at reduced pressure gave **5.1** (1.76 g, 65%).

Bp 65 °C @ *ca* 30 mmHg (lit¹⁶² 40–44 °C @ 20 mmHg).
¹H nmr δ 2.12 (s, 3H), 3.18 (s, 3H), 3.69 (s, 3H).

3-(Formylmethyl)-2,4-dimethylpenta-1,3-diene **5.2**



DMSO (1.011 mL, 14.26 mmol) in CH₂Cl₂ (10 mL) was added dropwise to a solution of oxalyl chloride (0.938 mL, 10.70 mmol) in CH₂Cl₂ (20 mL) at -78 °C. After stirring the clear solution for 5 min at -78 °C, a solution of the diene alcohol **2.22** (1.00 g, 7.13 mmol) in CH₂Cl₂ (10 mL) was added and the reaction was stirred at -78 °C for 30 min. Triethylamine (3.98 mL, 28.52 mmol) was added dropwise and after stirring for 5 min at -78 °C, the reaction was allowed to warm from -78 °C to 25 °C over a period of 30

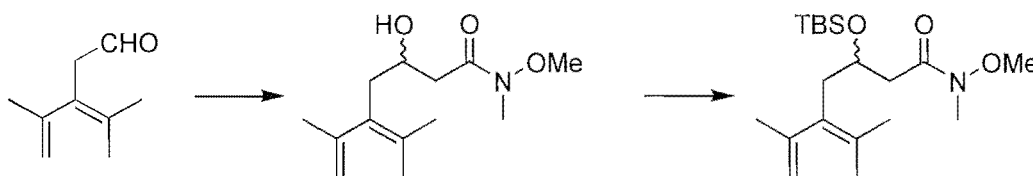
min. The reaction was quenched by the addition of saturated aqueous NH_4Cl (30 mL). The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2 (50 mL). The combined organic phases were washed with saturated aqueous NaHCO_3 (50 mL), saturated aqueous NH_4Cl (50 mL) and brine (50 mL), then dried (MgSO_4), filtered, and the solvent removed *in vacuo* to quantitatively yield **5.2** as a light brown oil (990 mg).

The unstable crude aldehyde had the following spectroscopic characteristics:

^1H nmr δ 1.69 (s, 3H), 1.76 (bs, 6H), 3.15 (t, 2H, $J = 1.0, 2.0$ Hz), 4.65 (m, 1H), 4.96 (m, 1H), 9.52 (t, 1H, $J = 2.5, 5.0$ Hz).

^{13}C nmr δ 20.16, 21.80, 22.15, 46.75, 114.27, 127.12, 131.56, 142.72, 145.97, 199.90.

(\pm)-3-[(2-*tert*-Butyldimethylsilyloxy)-4-(*N*-methoxy-*N*-methyl-carbamoyl)butyl]-2,4-dimethylpenta-1,3-diene **5.4**



N-Methoxy-*N*-methylacetamide **5.1** (1.150 g, 13.20 mmol) in THF (5 mL) was added dropwise to a solution of LDA (6.6 mL of 2.0 M in heptane/THF/PhEt (Aldrich), 13.20 mmol) in THF (50 mL) at -78°C . After stirring at -78°C for 15 min, aldehyde **5.2** (1.659 g, 12.00 mmol) in THF (5 mL) was added dropwise. The reaction was stirred at -78°C for 30 min before being quenched at -78°C with saturated aqueous NH_4Cl (20 mL). After warming to 25°C , the reaction mixture was extracted with diethyl ether (2 x 100 mL) and the combined organic phases were washed with brine (200 mL), dried (MgSO_4), filtered, and the solvent removed *in vacuo* to yield aldol adduct **5.3** as a pale red oil which was used directly.

An analytical sample of the aldol adduct could be obtained by flash chromatography on silica (50% EtOAc – petroleum ether):

^1H nmr δ 1.67 (s, 3H), 1.68 (s, 3H), 1.75 (s, 3H), 2.23-2.46 (m, 3H), 2.60-2.66 (m, 1H), 3.14 (s, 3H), 3.63 (s, 3H), 4.01-4.07 (m, 1H), 4.55 (m, 1H), 4.94 (m, 1H).

^{13}C nmr δ 20.10, 21.83, 22.41, 31.76, 37.35, 37.54, 61.06, 67.12, 113.89, 128.32, 132.87, 146.12, 173.78.

FTIR (CDCl_3 , cm^{-1}) 1068.5, 1093.6, 1253.6, 1463.9, 1471.6, 1641.3, 2856.4, 2929.7, 2956.7, 3411.8.

HRMS (EI) calc. for $\text{C}_{13}\text{H}_{23}\text{NO}_3$: 241.16779; found: 241.16803.

The crude aldol adduct (3.19 g) was dissolved in DMF (3 mL) and added to *tert*-butyldimethylsilyl chloride (1.990 g, 13.20 mmol) and imidazole (2.042 g, 30 mmol). The mixture quickly became homogenous and was stirred at 25 °C for 15 h. The reaction was diluted with H_2O (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with saturated aqueous NH_4Cl (20 mL), saturated aqueous NaHCO_3 (20 mL) and brine (20 mL). The organic phase was dried (MgSO_4), filtered, and the solvent removed *in vacuo* to yield a light red oil. Purification by flash chromatography on silica (17% EtOAc – petroleum ether) gave **5.4** as a clear oil (2.43 g, 57% over three steps).

^1H nmr δ -0.01 (s, 3H), 0.00 (s, 3H), 0.84 (s, 9H), 1.66 (s, 3H), 1.70 (s, 3H), 1.78 (bs, 3H), 2.27-2.42 (m, 2H), 2.61-2.68 (m, 1H), 3.15 (s, 3H), 3.67 (s, 3H), 4.23-4.32 (m, 1H), 4.61 (m, 1H), 4.98 (m, 1H).

^{13}C nmr δ -4.79, -4.70, 17.93, 20.32, 21.84, 22.67, 25.79, 31.93, 38.95, 39.53, 61.26, 69.17, 114.07, 127.90, 133.21, 145.96, 172.85.

FTIR (CDCl_3 , cm^{-1}) 1093.6, 1255.6, 1463.9, 1471.6, 1602.7, 1651.0, 2858.3, 2929.7, 2954.7.

HRMS (EI) calc. for $\text{C}_{18}\text{H}_{34}\text{NO}_3\text{Si}$ [$\text{M}^+ - \text{CH}_3$]: 340.23080; found: 340.23067.

(±)-3-[(2-*tert*-Butyldimethylsilyloxy)-4-oxo-but-5-enyl]-2,4-dimethylpenta-1,3-diene
5.5



Vinylmagnesium bromide (5 mL of 1.0 M in THF, 5 mmol) was added to a solution of the amide **5.4** (712 mg, 2 mmol) in THF (10 mL) at reflux. The reaction was heated at reflux for 1 h. After cooling to 25°C, the reaction was diluted with diethyl ether and saturated aqueous NH_4Cl (10 mL) was added and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 10 mL) and the combined organic phases were washed with saturated brine (30 mL), dried (MgSO_4), filtered, and the solvent removed *in vacuo* to yield a light yellow oil (412 mg, 69%). ^1H NMR analysis showed this oil to be essentially pure (>95%) enone. However, the enone was purified by flash chromatography on silica (20% EtOAc – petroleum ether) before further use to give **5.5** as a clear oil (333 mg, 56%).

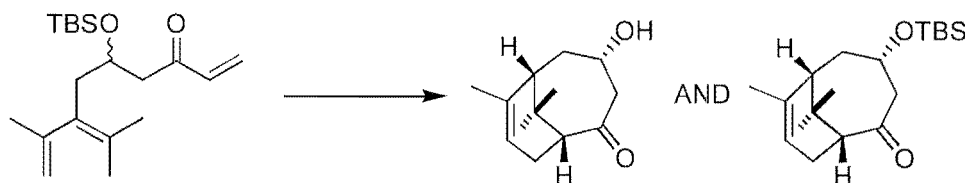
^1H nmr δ -0.04 (s, 3H), 0.03 (s, 3H), 0.82 (s, 9H), 1.67 (s, 3H), 1.70 (s, 3H), 1.78 (bs, 3H), 2.26-2.42 (m, 1H), 2.57 (dd, 1H, $J = 3.4, 14.7$ Hz), 2.72 (dd, 1H, $J = 8.3, 14.7$ Hz), 4.20-4.28 (m, 1H), 4.59 (m, 1H), 4.99 (m, 1H), 5.81 (dd, 1H, $J = 1.5, 10.3$ Hz), 6.19 (dd, 1H, $J = 1.5, 17.6$ Hz), 6.33 (dd, 1H, $J = 10.7, 18.1$ Hz).

^{13}C nmr δ -4.81, -4.49, 17.93, 20.34, 21.89, 22.61, 25.80, 29.69, 39.41, 46.41, 69.07, 114.18, 128.18, 133.08, 137.49, 145.90, 200.19.

FTIR (CDCl_3 , cm^{-1}) 1072.3, 1095.5, 1255.6, 1471.6, 1685.7, 2856.4, 2929.7, 2956.7.

HRMS It was not possible to obtain an accurate mass under a number of conditions

(±)-(2*R**,4*S**,6*S**)-2-Oxo-4-hydroxy-7,10,10-trimethylbicyclo[4.3.1]dec-7-ene **5.6**
and
(±)-(2*R**,4*S**,6*S**)-2-Oxo-4-(*tert*-butyldimethylsilyloxy)-7,10,10-trimethylbicyclo[4.3.1]dec-7-ene **5.7**



BF₃·OEt₂ (0.057 mL, 0.45 mmol) was added to a solution of the diene **5.5** (135 mg, 0.45 mmol) in CH₂Cl₂ (25 mL) at 0 °C. The reaction was stirred at 0 °C for 30 min before being poured into EtOAc – saturated aqueous NaHCO₃ (1:1, 50 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with H₂O (50 mL) and brine (50 mL), then dried (MgSO₄), filtered, and the solvent removed *in vacuo* to yield a pale yellow oil. Purification by flash chromatography on silica (20% EtOAc – petroleum ether) gave firstly silyl ether **5.7** (37 mg, 28%) and then alcohol **5.6** (56 mg, 41%).

Alcohol **5.6**

¹H nmr δ 1.00 (s, 3H), 1.03 (s, 3H), 1.85 (bs, 1H), 1.87 (bd, 3H, *J* = 2.4 Hz), 1.99-2.29 (m, 4H), 2.42-2.53 (m, 2H), 3.34 (dd, 1H, *J* = 9, 8, 12.2 Hz), 4.07 (m, 1H), 5.47 (bs, 1H).

¹³C nmr δ 23.03, 26.26, 26.88, 29.59, 33.01, 33.25, 46.07, 49.59, 56.71, 67.29, 119.65, 138.58, 212.87.

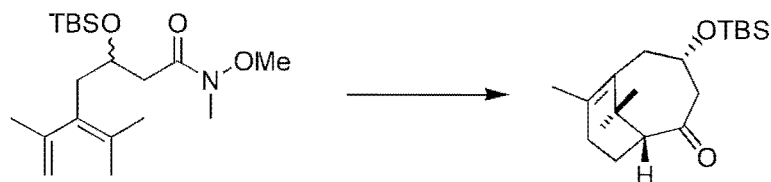
FTIR (CDCl₃, cm⁻¹) 1052.3, 1280.6, 1424.5, 1714.2, 2869.9, 3552.7.

HRMS (EI) calc. for C₁₃H₂₀O₂: 208.14633; found: 208.14636.

Selected data for silyl ether **5.7**

¹H nmr δ 0.01 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 0.97 (s, 3H), 1.00 (s, 3H), 1.77 (s, 1H), 1.86 (bs, 3H), 1.88-2.32 (m, 4H), 3.36-2.62 (m, 2H), 3.39 (t, 1H, *J* = 11.7 Hz), 5.42 (bs, 1H).

HRMS (EI) calc. for C₁₅H₂₅O₂Si [*M*⁺ - C₄H₉]: 265.16238; found: 265.16228.

(±)-(2*R,4*S**)-2-Oxo-4-hydroxy-7,10,10-trimethylbicyclo[4.3.1]dec-6(7)-ene 5.8**

Vinylmagnesium bromide (2.50 mL of 1.0 M in THF, 2.5 mmol) was added to a solution of the amide **5.5** (356 mg, 1 mmol) in THF (10 mL) at reflux. The reaction was heated at reflux for 1 h. After cooling to 25°C, the reaction was diluted with diethyl ether and saturated aqueous NH₄Cl (10 mL) was added and the layers were separated. The organic phases was washed with saturated aqueous NH₄Cl (20 mL), saturated aqueous NaHCO₃ (20 mL), brine (20 mL), dried (MgSO₄), filtered, and the solvent removed *in vacuo* to yield a light yellow oil. ¹H NMR analysis showed this oil to be essentially pure enone.

The crude enone was dissolved in CH₂Cl₂ (50 mL) and cooled to -78 °C. BF₃·OEt₂ (1.26 mL, 10 mmol) was added and the reaction was stirred at -78 °C for 1 h. The reaction was quenched by pouring into diethyl ether – saturated aqueous NaHCO₃ (1:1, 40 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (2 x 20 mL). The combined organic phases were washed with brine (50 mL), dried (MgSO₄), filtered, and the solvent removed *in vacuo* to yield a yellow oil. Purification by flash chromatography on silica (14% EtOAc – petroleum ether) gave **5.8** (137 mg, 43% for two steps).

¹H nmr δ 0.03 (s, 3H), 0.05 (s, 3H), 0.85 (s, 9H), 1.01 (s, 3H), 1.08 (s, 3H), 1.52-1.63 (m, 1H), 1.84 (s, 3H), 2.00-2.22 (m, 3H), 2.46-2.66 (m, 3H), 2.81-2.89 (m, 1H), 4.15 (m, 1H).

¹³C nmr δ -4.93, -4.76, 17.91, 22.20, 22.49, 25.73, 25.98, 28.06, 28.99, 36.11, 38.85, 51.05, 62.61, 70.43, 133.79, 135.27, 213.53.

FTIR (CDCl₃, cm⁻¹) 1057.6, 1273.6, 1421.7, 1719.9, 2869.2.

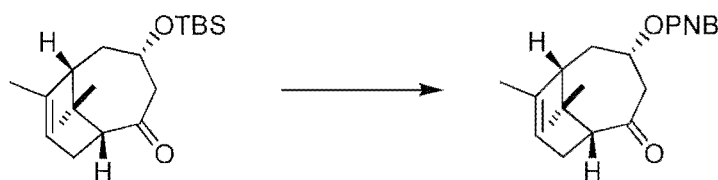
HRMS (EI) calc for C₁₉H₃₄O₂Si: 322.23281; found: 322.23323.

High Pressure IMDA Reactions

Reaction 1: Diene **5.5** (50mg, 0.17 mmol) was dissolved in the minimum volume of CH₂Cl₂. The solution was pressurized at 25 °C and 19 kbar for 24 h in a Psika High Pressure Reactor. After this period, the solvent was removed *in vacuo*. Analysis of the reaction by ¹H nmr showed an approximately 4:1 mixture of **5.8** and starting diene **5.5**.

Reaction 2: Diene **5.5** (25mg, 0.09 mmol) was dissolved in the minimum volume of CH₂Cl₂. The solution was pressurized at 55 °C and 16 kbar for 64 h in a Psika High Pressure Reactor. After cooling to 25 °C the solvent was removed *in vacuo*. Analysis of the reaction by ¹H nmr showed an approximately 2:2:1 mixture of **5.6:5.7:5.5**.

(±)-(2*R**,4*S**,6*S**)-2-Oxo-4-(4-nitrobenzoyloxy)-7,10,10-trimethylbicyclo[4.3.1]decane **5.9**



Tetra-*n*-butylammonium fluoride (1.58 mL of 1.0 M in THF, 1.58 mmol) was added dropwise to a solution of the silyl ether **5.7** (100 mg, 0.32 mmol) in THF (5 mL). After 3 h, TLC showed no further starting material. The reaction was diluted with EtOAc (20 mL) and quenched by the addition of saturated aqueous NH₄Cl (20 mL). The layers were separated and the organic phase was washed with saturated aqueous NaHCO₃ (20 mL) and saturated brine (20 mL), then dried (MgSO₄), filtered, and the solvent removed *in vacuo* to yield a light yellow oil. ¹H NMR analysis showed removal of the *tert*-butyldimethylsilyl group. The crude alcohol was dissolved in CH₂Cl₂ (5 mL), cooled to 0 °C and treated with Et₃N (0.122 mL, 0.88 mmol), DMAP (8 mg, 0.06 mmol), and 4-nitrobenzoyl chloride (65mg, 0.35 mmol, dissolved in 5mL CH₂Cl₂). The reaction was

stirred, with warming from 0 °C to 25 °C, for 12 h. The reaction was quenched with saturated NH_4Cl (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with saturated aqueous NaHCO_3 (40 mL), and brine (40 mL), then dried (MgSO_4), filtered, and the solvent removed *in vacuo* to yield a pale yellow solid. Purification by flash chromatography on silica (20% EtOAc – petroleum ether) gave **5.9** as a clear solid (36 mg, 32% for two steps).

A crystal suitable for X-ray analysis was obtained by recrystallization from 1:1 EtOAc – petroleum ether.

^1H nmr δ 1.06 (s, 3H), 1.11 (s, 3H), 1.92 (bs, 1H), 2.16-2.24 (m, 2H), 2.33-2.58 (m, 3H), 2.73 (dd, 1H, $J = 4.4, 11.7$ Hz) 3.44 (dd, 1H, $J = 9.8, 11.7$ Hz), 5.37 (m, 1H), 5.50 (bs, 1H), 8.13 (d, 2H, $J = 8.8$ Hz), 8.27 (d, 2H, $J = 8.8$ Hz).

^{13}C nmr δ 23.05, 26.63, 27.04, 29.42, 30.42, 32.84, 45.31, 46.11, 56.64, 70.57, 119.63, 123.51, 130.64, 135.55, 137.00, 150.56, 163.65, 211.03.

FTIR (CDCl_3 , cm^{-1}) 1105.1, 1280.6, 1463.9, 1525.6, 1699.2, 1716.5, 2854.5, 2954.7.

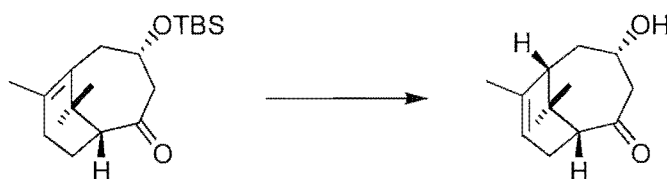
HRMS (EI) calc. for $\text{C}_{20}\text{H}_{23}\text{NO}_5$: 357.15762; found: 357.15793.

Crystal data and structure refinement for **5.9**

Identification code	apabm	
Empirical formula	$\text{C}_{18}\text{H}_{22}\text{NO}_5$	
Formula weight	332.37	
Temperature	162(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	$a = 7.011(2)$ Å	$a = 83.099(4)^\circ$.
	$b = 7.292(2)$ Å	$b = 83.957(4)^\circ$.
	$c = 18.357(6)$ Å	$\gamma = 73.564(4)^\circ$.
Volume	$891.0(5)$ Å ³	
Z	2	
Density (calculated)	1.239 Mg/m ³	
Absorption coefficient	0.090 mm ⁻¹	
F(000)	354	
Crystal size	$.14 \times .42 \times .8$ mm ³	
Theta range for data collection	3.03 to 26.41° .	

Index ranges	-8<= <i>h</i> <=8, -3<= <i>k</i> <=8, -22<= <i>l</i> <=22
Reflections collected	4223
Independent reflections	3256 [R(int) = 0.0284]
Completeness to theta = 26.41°	89.0 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3256 / 0 / 238
Goodness-of-fit on F ²	0.888
Final R indices [I>2sigma(I)]	R1 = 0.0435, wR2 = 0.1016
R indices (all data)	R1 = 0.0793, wR2 = 0.1116
Largest diff. peak and hole	0.326 and -0.236 e.Å ⁻³

Conversion of (±)-(2*R**,4*S**)-2-Oxo-4-(*tert*-butyldimethylsilyloxy)-7,10,10-trimethylbicyclo[4.3.1]dec-6(7)-ene **5.8** to
(±)-(2*R**,4*S**,6*S**)-2-Oxo-4-hydroxy-7,10,10-trimethylbicyclo[4.3.1]dec-7-ene **5.6**



BF₃·OEt₂ (0.012 mL, 0.1 mmol) was added to a solution of Diels–Alder adduct **5.8** (15 mg, 0.05 mmol) in CH₂Cl₂ (1 mL) at 0 °C. The reaction was stirred, with warming from 0 °C to 25 °C over a period of 1 h and then quenched by the addition of saturated aqueous NaHCO₃ (5 mL) and EtOAc (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (5 mL). The combined organic phases were washed with brine (10 mL), dried (MgSO₄) and the solvent removed *in vacuo* to yield a yellow oil. ¹H NMR analysis showed two compounds in *ca* 2.5:1 ratio. One was the desired compound **5.6** (minor component) and the other was not characterized.

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